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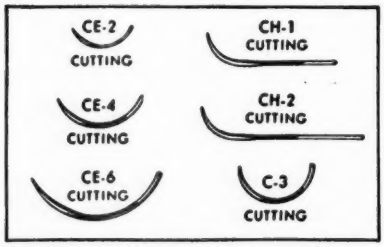

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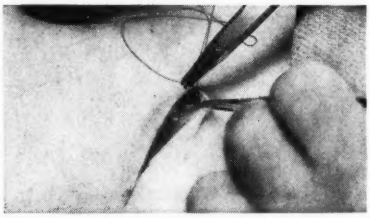

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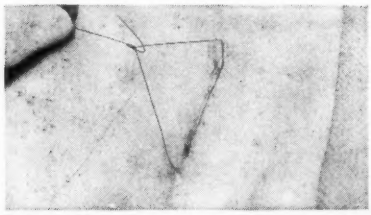

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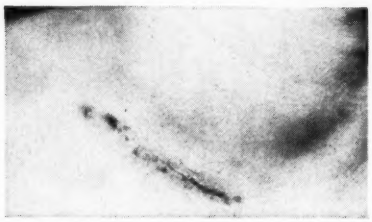

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 98 FEBRUARY, 1954 NUMBER 2

GUNSHOT WOUNDS OF MAJOR ARTERIES

An Experimental Study with Clinical Implications

HORACE G. MOORE, JR., M.D., Wilmington, North Carolina, LLOYD M. NYHUS, M.D., EDMUND A. KANAR, M.D., and HENRY N. HARKINS, M.D., F.A.C.S., Seattle, Washington

THEODOR BILLROTH, a talented Viennese surgeon of the last century and a man of protean interests, traced the early development of the treatment of gunshot wounds. This work was published in 1859 under the title, "Historical Studies on the Nature and Treatment of Gunshot Wounds from the Fifteenth Century to the Present Time." He cited the statement of the historian Villiani that the use of gunpowder in warfare was first mentioned in the year 1338. According to Billroth, the oldest work on surgery written in German contained a short chapter on gunshot wounds. This was written by Hieronymus Brunschwig of Strassburg in 1497 and began thus, "Dis ist das buch der cirurgia handwürckung der wundartznei vō Hyeraimo Braūschweig." The surgery of gunshot wounds described in Billroth's work was mainly concerned with débridement, bullet removal, amputation, and skull trephination.

It is not surprising that surgeons of the last century spent little of their efforts on the study of gunshot wounds of major arteries. Most probably there were few patients with such injuries who survived long enough to be treated surgically. The feasibility of surgical repair of arterial gunshot wounds had to await such products of the twentieth century: as (1) the treatment of shock, (2) good anesthesia, (3) ready availability of surgical care (rapid, efficient evacuation of the wounded in the case of the military), (4) antibiotics, (5) sound preoperative and postoperative care, and (6) good technique of blood vessel suture.

Now that such important adjuncts are available to help the patient with arterial injury reach the surgeon alive, it is the surgeon's duty to know how to treat this injury with minimal loss of life and limb. Furthermore, the frequency of gunshot injuries, both civilian and military, is greater now than in the past.

For these reasons it seems appropriate to seek answers to the following questions: (1) What is the nature and extent of injury in arterial gunshot wounds? (2) How much débridement is necessary? (3) Is repair feasible? (4) What is the best method of repair of such wounds?

CLINICAL REPORTS

The literature on the subject of gunshot wounds of major arteries is mostly clinical in nature. As far as we have been able to

From the Department of Surgery of the University of Washington School of Medicine, and the King County Hospital, Seattle, Washington.

This work was aided in part by a Grant-in-Aid (H-1136) from the National Institutes of Health, Bethesda, Maryland.

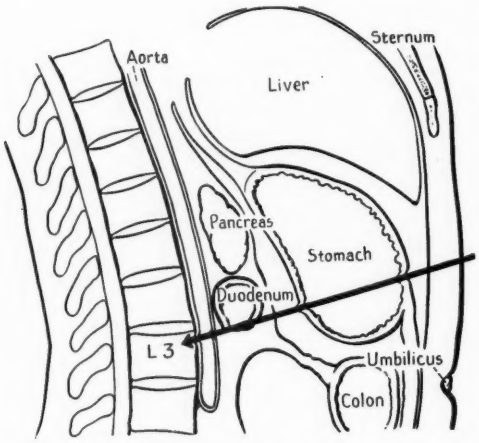

Fig. 1. Diagrammatic representation of the path of the bullet in the personal case. Note that bullet entered midline of abdomen 3 inches above the umbilicus, perforated the anterior and posterior walls of the stomach, nicked the duodenum, perforated the aorta, and lodged at the level of the upper portion of the third lumbar vertebra.

determine, there are no reported experimental studies. A few of the pertinent reports will be considered briefly here.

Kornblith reported an instance of a patient who was shot in the abdominal aorta with a .22 caliber missile. At surgical exploration the defects were seen to be plugged with clot, which was not disturbed. The patient lived for 9 days and died of hypostatic pneumonia. Kornblith stated that the defects were in the form of small stellate holes.

In 1943, Langley of England reported the case of a 23 year old gunner in the Air Corps who sustained an injury of the innominate artery, caused by perforation of the vessel with a cannon-shell fragment. The patient was brought to the hospital 5½ hours after injury and presented a picture of deep shock, but with no active bleeding. X-ray examination showed the fragment to be cuboidal in shape and 1 centimeter in diameter. This patient was operated upon 12½ hours after injury. The perforations were at the bifurcation of the innominate artery and sealed by clot. The anterior perforation was closed without any débridement, but the posterior defect was "more ragged." The tissue would not support sutures, and finally attempts at repair were abandoned. The injured segment was then resected and ligated. This patient died of pulmonary edema 16 hours postoperatively. Bradford and Johnston reported the case of a 21 year old man with a traumatic rupture of the lower thoracic aorta, who survived for 81 days. Kastl cited the instance of a 33 year old man who survived for 10 days after complete transection of the aorta just below the left subclavian artery.

On the basis of his military experience in South Africa, Makins in 1901 divided arterial gunshot wounds into two main types: (1) contusion or laceration of one or more layers of the vessel without perforation, and (2) perforation of the vessel, either as a tangential nick or a more centrally placed through-and-through wound.

Learmonth made the important clinical observation that intimal damage is almost always greater than external inspection of the vessel would indicate. In the case of contused arteries without perforation, the intima may be cracked and fissured. Linton and Leslie also noted this characteristic of arterial injury. Learmonth further stated that if a transverse wound of an artery occupies more than one-third of the circumference, it would be preferable to complete division of the vessel and perform a complete anastomosis. In this way correct alignment of the long axis of the vessel could be better preserved. Herrmann was often able to observe a systolic murmur as evidence of distortion of the line of flow when partial transverse suture was used.

In 1942, Holman of San Francisco stated: "The suturing of a wounded artery is notoriously disappointing because of immediate thrombosis. Should the suture on rare occasions be successful, the late development of aneurysm and pain is the usual end-result." In 1943, Gage of New Orleans reemphasized the importance of intimal damage in arterial injuries. He also observed that vessels that are more securely fixed anatomically are more likely to be injured.

Maybury reported that axial anastomosis of an artery severed by a high velocity mis-

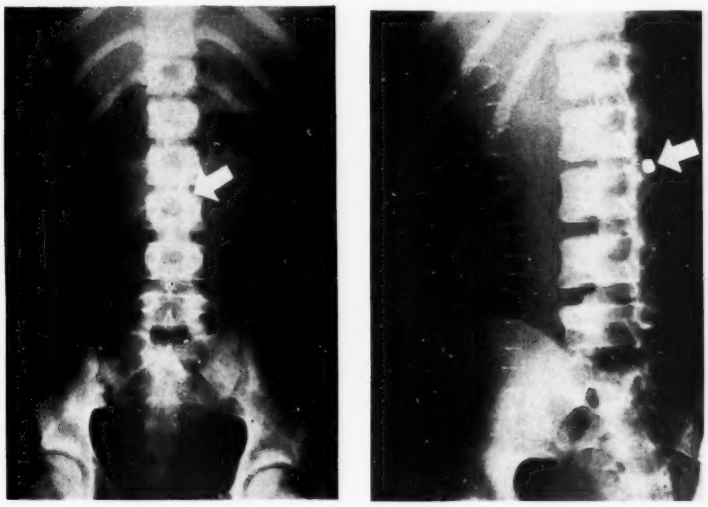

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Fig. 2. Roentgenograms of patient's spine. Bullet fragments are indicated by arrows. a, Anterior-posterior view. b, Oblique view. The row of buried steel wire sutures used to close the abdominal wall is visible.

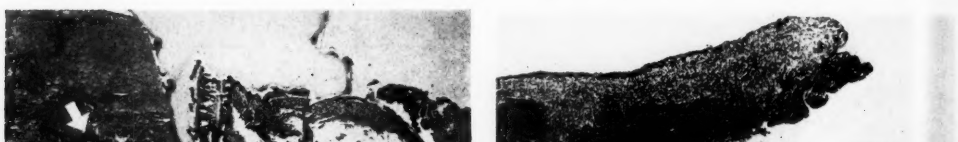
sil is seldom possible. This he attributed to damage to the severed ends of the vessel caused by the "lateral concussive effect" of the missile. Concerning lateral arterial gunshot wounds, Maybury said that suture was not often possible. He mentioned that longitudinal suture of a vessel always leads to undesirable narrowing of the lumen. Lam of Detroit reported that in repairing an arteriovenous fistula, he attempted to suture the vessel longitudinally, but such severe stenosis occurred that before closing he resected the segment and performed an anastomosis.

The late complications of arterial gunshot wounds such as aneurysm and arteriovenous fistula have been discussed by many authors.

It is of interest that Miller and Welch, in studying the duration of ischemia of extremities in the dog as related to survival of the extremity, found the following results: (1) ischemia for 1 to 6 hours gave 90 per cent survival; (2) ischemia for 12 to 18 hours gave 50 per cent survival; (3) ischemia for 24 hours or longer gave 20 per cent survival.

Beebe and DeBakey studied the distribution of arterial injuries and frequency of amputation among the United States troops during World War II. They found that arterial injuries in the lower extremity were more serious than those in the upper extremity in that 50 per cent of the former and 24 per cent of the latter required amputation. They found that 37 per cent of such injuries necessitated amputation when 10 hours elapsed before treatment, 49 per cent when the lag was between 10 and 20 hours, and 63 per cent when more than 20 hours elapsed. Beebe and DeBakey reported that among the 174,000 wounds of World War I, 443 were arterial wounds with a 25 per cent mortality (109 deaths).

Recently Jahnke and Howard reported their experiences with major arterial injuries in the Korean War. Since they began to use the technique of arterial repair only 10.3 per cent of their patients required amputation. They stated that this figure is in contrast to an amputation rate of 49 per cent during World War II when ligation was the treatment of choice in arterial injuries. Jahnke and Howard stated: "The extent of damage was not always easily determined. Grossly roughened intima was considered a definite sign of damage, and débridement was car-



a b

Fig. 3. Photomicrograph of aortic repair of patient. Arrow indicates suture. Note extensive fragmentation of the wall. Intimal side is up. a, Hematoxylin and eosin stain. b, Verhoeff's stain. ×23.

ried beyond such an area to a point approximately 1 centimeter into apparently normal vessel." In most instances they excised the injured segment and performed an anastomosis although autogenous vein grafts were used in 8 instances and transverse suture in 2 cases out of a total of 58 cases.

Thus, it is seen that arterial gunshot wounds are not rare. Enough patients survive and reach surgical aid to justify clinical and experimental observations to improve the care that such patients receive.

PERSONAL CASE REPORT

The patient was a 14 year old white girl who was admitted to the King County Hospital, Seattle, at 7:30 p.m., May 5, 1952. Thirty minutes prior to admission she had shot herself in the abdomen with a .22 caliber rifle. She was in deep shock on admission with no obtainable blood pressure or palpable radial pulse. Her femoral pulse was weak and thready with a rate of 140 beats per minute. There was a small hole of entrance in the midline of the abdomen 3 inches above the umbilicus. The wound was surrounded by powder burns. The abdomen was moderately distended to inspection, dull to percussion, and doughy to palpation. No bowel tones were audible. Femoral pulses were bilaterally weakly palpable. There was no hole of exit. Gross voluntary movement was observed in both lower extremities.

TABLE I.—SPECIFICATIONS OF MISSILES USED IN EXPERIMENTS

Caliber	Weight (grains)	Muzzle velocity (feet/second)
.177*	10	180–500
.22 short	29	1125
.22 long rifle	40	1335

*This missile was propelled by compressed air from an air pump pistol pumped 8 times. If shot within 5 seconds of the time of pumping, the muzzle velocity was 455-500 feet per second. One minute after pumping, the muzzle velocity dropped to 250-275 feet per second. Five minutes after pumping it was 180 feet per second. Unfortunately, we have no measurements of time elapse between pumping and shooting as we did not foresee the significance of the time factor. However, we think that all injuries with this type of missile were made within 5 minutes of the time of pumping.

Whole blood was ordered from the blood bank immediately and plasma was started intravenously in the meantime. When the blood arrived, 200 cubic centimeters was given intra-arterially in the right radial artery, following which she began to respond and answer questions. It is of interest that 1,000 cubic centimeters of blood was rapidly administered to her intravenously prior to the small intra-arterial transfusion without any apparent response. After 200 cubic centimeters of blood had been given into the radial artery, it began to extravasate and, therefore, the remainder was given intravenously. After she received 2,000 cubic centimeters of blood, her blood pressure rose to 65/50 and the pulse rate was 140 beats per minute.

A gastric tube was inserted and a large amount of "coffee-ground" material was aspirated. In spite of continued rapid administration of whole blood, the blood pressure remained 65/50 until she was taken to the operating room. An x-ray film of the abdomen showed the fragmented bullet lying just to the left of the midline at the level of the second lumbar intervertebral space and the upper portion of the third lumbar vertebra. The course of the missile and her state of profound shock suggested the possibility of aortic damage.

At 1:10 a.m., May 6, 1952, 6⅙ hours after injury, she was operated upon by one of us (H.G.M., Jr.). A midline incision 30 centimeters long was made. There was a small amount of free blood and gastric and intestinal contents in the peritoneal cavity. There was a large retroperitoneal hematoma which had dissected into the right mesocolon and entire

right side of the retroperitoneal space. The right side of the colon was mobilized extensively to the left exposing the retroperitoneal space. Large handfuls of clotted blood were evacuated and a 0.4 centimeter perforation on the right anterior surface of the aorta was seen to be bleeding freely. Bleeding was controlled by digital pressure over the defect without occluding flow through the aorta. The adjacent aorta was dissected sufficiently to allow the application of vascular clamps proximally and distally. The patient's blood pressure rose to normal levels immediately. The aortic wound could then be inspected satisfactorily for the first time. Two holes were seen to be eccentrically located on the right side of the aorta, each measuring 0.4 centimeter in diameter. The two holes were separated by a thin tenuous bridge of aortic tissue. The edges of the defects had finely ragged margins. The bridge of tissue and the ragged protrusions from the defect edges were débrided, thus converting the two defects into one hole about 1 centimeter in diameter. This wound was then sutured transversely with a continuous Carrel stitch of No. 5-0 silk on an atraumatic needle. When the clamps were removed, hemostasis was satisfactory, and there was good flow through the site of repair. The time of occlusion was not measured but it was estimated to be about 30 minutes. At this time the patient's general condition seemed good.

Attention was next turned to exploration for other intra-abdominal injury. There was a small perforation in both the anterior and posterior walls of the gastric antrum. There was also a tangential perforation of the third portion of the duodenum. Parenthetically, it is worthy of note that unless the duodenum had been mobilized extensively, this perforation would not have been detected. The entire right half of the colon and its mesentery appeared as a large hematoma although no actual perforation of the colon or its mesentery could be discerned. The remainder of the exploration disclosed no further injury. The two defects in the stomach and the one in the duodenum were closed. In addition, a right hemicolectomy with an ileotransverse-colic anastomosis was performed. During the preoperative and operative periods the patient received 9,500 cubic centimeters of whole blood. Figure 1 is a diagrammatic representation of the path of the bullet.

During the first postoperative day she developed bronchopneumonia which responded to antibiotic therapy. After the first day she became stabilized as far as shock was concerned. Her fluid and electrolyte balance was carefully managed, and a satisfactory urinary output was maintained.

On the fourth postoperative day, she complained of some numbness and tingling of her legs associated with difficulty in movement of her feet. Objectively there was complete loss of sensation in the left foot and impairment of flexion and extension of the left foot. Knee jerks and ankle jerks were absent bilaterally. A spinal tap revealed

TABLE II.—TYPES OF EXPERIMENT USED TO STUDY NATURE AND EXTENT OF INJURY

Group	Blood pressure			Aorta exposed to		
	Hypotensive	Normotensive	Hypertensive	Air	Saline	Tissue
I		X		X		
II	X			X		
III			X		X	
IV		X			X	
V		X				X

xanthochromic fluid and no evidence of a block, as determined with the Queckenstedt test. Roentgenograms of the spine, as seen in Figure 2a and b, showed the bullet fragments at the level of the second and third lumbar vertebrae. The largest fragment was located posteriorly near the tip of the spinous process. There was a smaller fragment in the left posterior part of the spinous canal. Several tiny fragments were located about a tiny undisplaced fracture in the region of the articular facets between the second and third lumbar vertebrae on the left. It was decided that surgical intervention for her spinal injury was not indicated. On May 11, 1952, a cystometrogram was normal. Tests of motor function showed weakness of the left hip adductors and hamstrings and no abduction of the left hip. Quadriceps action on the left was absent. It was concluded that these neurologic changes were caused by the bullet entering the spinal canal and that these changes were irreversible.

On May 12, 1952, it was noted that the patient was jaundiced. Her total serum bilirubin was 9.0 milligrams per cent. The jaundice reached its peak on May 15, 1952, at a level of 29 milligrams per cent. On May 27, 1952, it had declined to 3.3 milligrams per cent. The remainder of the laboratory studies yielded equivocal indications of the type of jaundice with which we were dealing. It was suggested that her jaundice might be due to a combination of the following three factors: (1) incompatibility of transfused blood with some

TABLE III.—TYPES OF EXPERIMENT USED TO STUDY DÉBRIDEMENT AND REPAIR

Group	Débridement				Repair		
	None	Ragged edges	Wedge	Resect segment	Transverse suture	Longitudinal suture	Anastomosis
VI	X				X		
VII	X					X	
VIII		X				X	
IX			X		X		
X				X			X

TABLE IV.—DATA FROM GROUP I DOGS (NORMOTENSIVE WITH AORTA EXPOSED TO AIR)

Dog No.	Site of aortic injury	Missile	Size of defects, centimeters	Comment
A-16*	Abdominal	.177	ant.: 0.4 post.: 0.5 External	Anterior and posterior longitudinal slits; intimal damage greater
A-12	Abdominal	.177	ant.: 0.7 post.: 0.9 External	Anterior and posterior longitudinal slits; intimal damage greater
A-11	Abdominal	.177	ant.: 0.4 post.: 0.5 External	Anterior and posterior longitudinal slits; intimal damage greater
E-79	Abdominal	.177	ant.: 0.5 post.: 0.4 External	Anterior and posterior longitudinal slits; intimal damage greater
A-14	Abdominal	.177	post. Internal: 0.8 External: 0.6	Anterior and posterior longitudinal slits; intimal damage greater
A-13	Abdominal	.177	ant. Internal: 0.6 External: 0.3 post. Internal: 0.5 External: 0.4	Anterior and posterior longitudinal slits; intimal damage greater
I	Thoracic	.177	ant.: 0.5 post.: 0.4 External	Anterior and posterior longitudinal slits; intimal damage greater
A-35	Thoracic	.177	ant.: 0.5 post.: 0.5 External	Anterior and posterior longitudinal slits; intimal damage greater
A-21	Abdominal	.177	ant.: 0.6 post.: 0.5 External	Anterior and posterior longitudinal slits; intimal damage greater
E-98	Thoracic	.177	ant.: 0.4 post.: 1.05 External	Anterior and posterior longitudinal slits; intimal damage greater
A-32	Thoracic	.177	ant.: 0.45 post.: 0.70 External	Anterior and posterior longitudinal slits; intimal damage greater
A-3	Thoracic	.22 short	ant.: 4.2 x 1.2 post.: 3.2 x 0.8 External	Extensive comminuted anterior and posterior wounds; intimal damage more extensive
2	Thoracic	.22 short	Comparable in size to A-3	Extensive comminuted anterior and posterior wounds; intimal damage more extensive
3	Thoracic	.22 short	Comparable in size to A-3	Extensive comminuted anterior and posterior wounds; intimal damage more extensive
4**	Thoracic	.22 short	Comparable in size to A-3	Extensive comminuted anterior and posterior wounds; intimal damage more extensive
5	Thoracic	.22 short	Comparable in size to A-3	Extensive comminuted anterior and posterior wounds; intimal damage more extensive

*See Figure 4.
**See Figure 5a and b.

hemolysis, (2) absorption of extravasated blood, and (3) liver damage secondary to profound shock. Whatever the cause, her jaundice was spontaneously disappearing.

On May 27, 1952, 22 days after her injury, she began to pass grossly bloody material per rectum. For the next 2 days bloody stools were intermittently passed. On May 29, 1952, she went into shock, and after vigorous transfusion therapy she was again operated upon. It was found that the aortic repair had disrupted and was once again bleeding profusely. The third portion of the duodenum was inextricably adherent to the subjacent aorta although no actual communication between the aorta and duodenal lumen could be demonstrated. Because of the dense adhesions it was impossible to gain adequate control of the aorta and the bleeding continued. She developed cardiac arrest, and, in spite of immediate thoracotomy and attempted cardiac resuscitation, she expired. During her entire hospital stay she received 27,000 cubic centimeters of whole blood.

Concerning the breakdown of the aortic suture line with bleeding from the intestinal tract, the following 2 instances from the literature are pertinent: (1) Worgan reported the case of a 50 year old man with rupture of the aorta into the third portion of the duodenum. At autopsy there was dense adherence between the duodenum and the aorta. Worgan attributed the rupture to ulceration of the aorta at the site of an arteriosclerotic plaque. (2) Coggeshall and Genovese found, in the literature, 36 instances of rupture of an aortic aneurysm into the

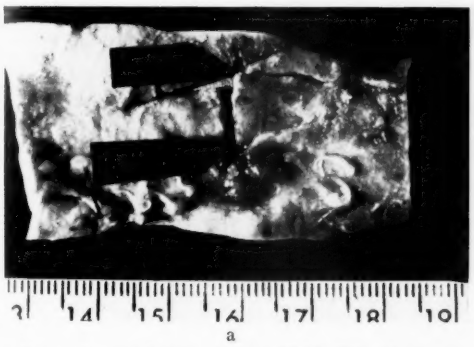
duodenum. They were able to find a total of 49 cases in which an aortic aneurysm had ruptured into the gastrointestinal tract. They reported a case of their own in which there was a severe retroperitoneal hematoma from rupture of an aortic aneurysm. There was associated massive gastrointestinal bleeding. At autopsy the jejunum was densely adherent to the aorta, but no communication could be identified. They postulated that bleeding into the root of the mesentery might have caused sufficient venous tamponade to cause congestive bleeding from the jejunum. Whether such a mechanism could account for the gastrointestinal bleeding in our patient is open to conjecture.

Figure 3a and b is a photomicrograph of the site of aortic repair in our patient. Marked fragmentation of the vessel wall in the vicinity of repair is the outstanding feature in these microscopic sections. The following three aspects of this case report are worthy of special emphasis: (1) A patient with severe injury involving a gunshot wound of the abdominal aorta lived long enough to receive surgical repair of the aorta. (2) The repair was unsatisfactory. (3) There is need for experimental work designed to elucidate the principles of proper repair of such injuries. These principles must be based upon knowledge of the nature and extent of injury in gunshot wounds of major arteries. It was because of these considerations that we undertook the experiments described as follows.

Fig. 4. Operative view of abdominal aortic gunshot wound of dog A-16. Injured with .177 caliber missile (see Table IV).

METHOD OF EXPERIMENTAL STUDY

General methods. Mongrel dogs weighing between 5 and 32 kilograms were used in this study. Although it is hoped that the findings in this experimental work will apply to all arteries worthy of repair, we confined our studies to the thoracic and abdominal aorta. We did so because the size of these arteries in the dog most closely approximates that of significant arteries involved in clinical injuries. All dogs were anesthetized with intravenous veterinary nembutal, and the animals subjected to thoracotomy were given supplementary endotracheal ether and oxygen by mechanical respirator.



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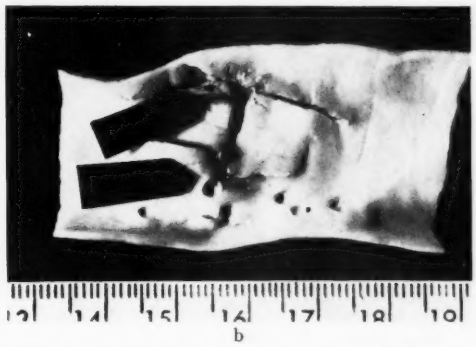
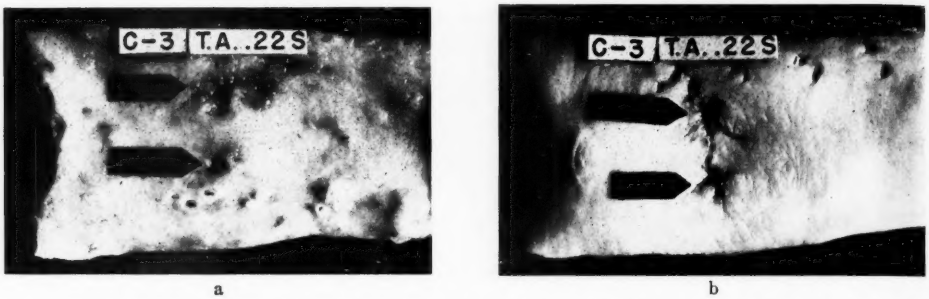


b

Fig. 5. Group I injury of dog 4 (Table IV). Normotensive thoracic aorta injured with .22 caliber short missile when exposed to air. Intimal damage is greater than apparent external damage. This is extensive splitting type of injury. a, External view. Anterior defect at upper arrow. b, Internal view. Anterior defect at upper arrow.



a b

Fig. 6. Group II injury of dog C-3 (see Table V). Hypotensive thoracic aorta injured with .22 caliber short missile when exposed to air. Intimal damage is greater than external damage. This injury is in the form of small stellate holes. a, External view. Anterior defect at upper arrow. b, Internal view. Posterior defect at upper arrow.

Three types of missiles were used in all experiments (Table I). When repair of the defect was anticipated, the operative procedure was carried out with aseptic technique. When repair was planned, the aorta was freed of its branches and surrounding tissue prior to injury for a distance of 7 to 12 centimeters. Otherwise the unfreed aorta was shot. The firearm muzzle was always placed between 1 and 3 feet from the vessel. In those injuries that were repaired No. 5-0 black silk on an atraumatic needle was used in the form of a continuous Carrel suture. Anticoagulants were not utilized in any of our experiments.

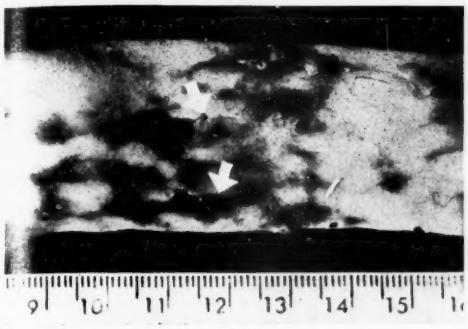
It will be noted that there is some overlap in the use of dogs in that some of the animals used to study débridement and repair were also included in one of the groups used to study the nature and extent of injury. Also in a few instances the thoracic aorta was injured for one part of the study and the abdominal aorta for another part. This accounts for any duplication of dog identification numbers from one group to another.

TABLE V.—DATA FROM GROUP II DOGS (HYPOTENSIVE WITH AORTA EXPOSED TO AIR) INJURY TO THORACIC AORTA

Dog No.	Size of defects, centimeters	Comment
A-13	ant. Internal: 0.14 External: 0.05 post. Internal: 0.16 External: 0.10	Small anterior and posterior stellate defects; intimal damage more extensive
E-55	ant. Internal: 0.7 External: 0.5 post. Internal: 0.5 External: 0.4	Small anterior and posterior stellate defects with connecting intimal fracture
C-3*	Comparable to E-55	Small anterior and posterior stellate defects with connecting intimal fracture
4	Comparable to E-55	Small anterior and posterior stellate defects; intimal damage more extensive
5	ant. Internal: 0.5 External: 0.2 post. Internal: 0.5 External: 0.2	Small anterior and posterior stellate defects; intimal damage more extensive

In all instances, except dog A-13 in which .177 caliber was used, a .22 cailber short missile was utilized.
*See Figure 6a and b.

Nature and extent of injury. Five groups of animals were used in this part of the experiment as summarized in Table II. In order to evaluate the configuration and size of the wounds we took photographs and measurements of most of the injuries. We sought to evaluate the effect of normal surrounding tissue on the nature and extent of injury by shooting the aorta of 2 intact dogs (group V). In group IV the aorta was covered with a shallow layer of physiologic saline solution 1.5 to 2.5 centimeters deep as a replacement for normal body tissues. (This was desirable because of the difficulty in hitting the aorta of the intact dog.) In group I the aorta was exposed to air as a control for the influence of surrounding tissue. In group II the aorta was hypotensive and exposed to air and in group III the aorta was hypertensive and exposed to saline in order to study the effects of variations in blood pressure at the time of injury. To some extent we have studied the effects of different missile weights and velocities within the limited range outlined in Table I. Most of the injured aortas were studied microscopically in groups I to V inclusive. We made hematoxylin and eosin and Weigert's elastic tissue stains of all specimens.



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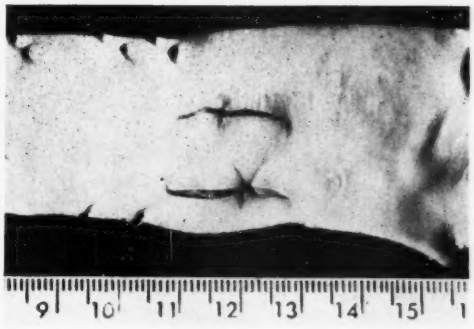


b

Fig. 7. Photograph of group III injury of dog A (see Table VI). Note the longitudinal character of the defect. The anterior defect is on top. The arrows indicate the defects seen externally. a, External view. b, Internal view.

Débridement and repair. Of necessity the type of repair will have to depend largely upon the type of débridement employed. All of the .22 caliber missile injuries that were repaired were achieved with the aorta surrounded by a shallow layer of physiologic saline solution as previously discussed. All of the repaired .177 caliber injuries were made with the aorta exposed to air. All of the injuries in this portion of the study were group IV wounds. It was believed that this layer of saline would act in much the same manner as the normal surrounding body tissue, since the latter has approximately the same density as physiologic saline. Such an expedient was necessary because of the difficulty in hitting the aorta in the intact dog.

As stated previously, the aorta was freed before injury in groups VI to X inclusive, and immediate hemostasis was achieved after injury by the application of vascular clamps above and below the wound. The occlusion time was measured accurately in all instances in which repair was achieved.

When repair was accomplished, the animals were allowed to survive for varying periods of time. At the time of death or sacrifice, the specimens were examined grossly and microscopically and photographs were taken with the vessel inflated to 120 millimeters of mercury with air and later with them opened longitudinally. Some of the animals with successful repairs were studied with aortograms, using 70 per cent diodrast.

Table III outlines the types of débridement and repair used in groups VI to X inclusive. In group VIII where only the ragged edges of the defects were débrided, only enough tissue to make the defect margins smooth was removed. In group IX, the term "wedge débridement" applies to removal of the part of the circumference of the vessel containing the defects, i.e., part of the wall was left in continuity. Each of the animals surviving repair was given 300,000 units of penicillin daily for 2 to 4 days.

TABLE VI.—DATA FROM GROUP III DOGS (HYPERTENSIVE WITH AORTA EXPOSED TO SALINE) INJURY TO THORACIC AORTA

Dog	Blood pressure	Size of defects, centimeters	Comment
A*	200/130	ant. Internal: 2.0, External: 1.2; post. Internal: 2.0, External: 0.5	Long anterior and posterior longitudinal defects; intimal damage more extensive
B	250/150	ant. Internal: 0.2, External: 0.2; post. Internal: 2.0, External: 1.9	Small stellate anterior defect, both internal and external. Long longitudinal posterior defect
C	280/175	ant. Internal: 2.7, External: 2.2; post. Internal: 1.6, External: 1.6	Long longitudinal anterior and posterior defects
D	320/150	ant. Internal: 0.6, External: 0.4; post. Internal: 1.2, External: 0.7	Stellate defect anterior, but larger than seen in normotensive injury under the same conditions. Longitudinal component to intimal injury of posterior defect

A .22 caliber short missile was used in all these experiments.
*See Figure 7a and b.

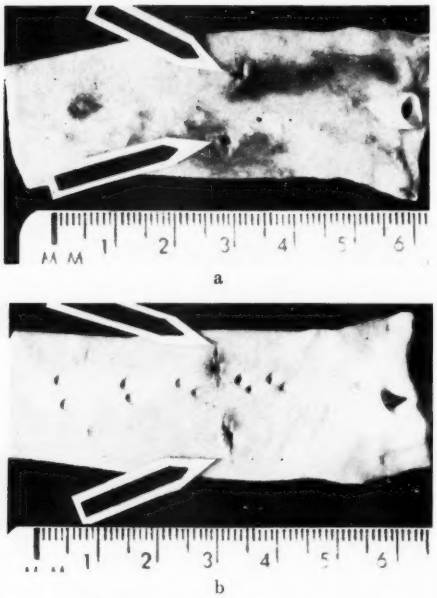


Fig. 8. Photograph of group IV injury of dog H (see Table VII). Normotensive thoracic aorta injured with .22 caliber long rifle missile when exposed to saline. Note the small stellate holes and that intimal damage is more extensive than external injury. a, External view. Anterior defect at upper arrow. b, Internal view. Posterior defect at upper arrow.

RESULTS OF EXPERIMENTAL STUDY

Nature and extent of injury. Pertinent details of the protocols for the individual animals in this portion of the study may be found in Tables IV through VIII. The characteristic findings for each group as a whole will be given as follows:

Group I (Table IV). Sixteen animals were injured in this group, 5 of them being shot with .22 caliber short missiles and the remaining 11 with .177 caliber missiles. The .177 caliber injuries were in the form of small longitudinal anterior and posterior slits averaging 0.5 to 0.6 centimeter in length. The edges were finely ragged and the intimal damage was always slightly more extensive than the apparent external damage. Figure 4 is a photograph of such an injury taken at the time of surgery (dog A-16). The injuries in the 5 aortas shot with .22 caliber short missiles were explosive and extensive. The aortic wounds were 6 to 8 times as large as the .177 injuries of this group. Intimal damage was more extensive than was apparent from external inspection. In several of the animals the intimal damage was continuous between the anterior and posterior holes. A typical .22 caliber short injury from this group is shown in Figure 5a and b (dog 4).

Group II (Table V). There were 5 animals subjected to injury in this group. All but 1 of the injuries were achieved with .22 caliber short missiles. The other was injured with a .177 caliber projectile. These wounds were strikingly smaller than those of group I and generally took the form of small stellate anterior and posterior defects with finely ragged edges. In each instance, however, the extent of gross intimal damage was greater than was externally apparent. Figure 6a and b shows a typical .22 caliber short injury of this group (dog C-3).

Group III (Table VI). Four aortas were shot with .22 caliber missiles while in a hypertensive state. An intravenous drip of norepinephrine solution was given during the period of wounding. Blood pressure recordings were made throughout the experiment with use of a Sanborn polyviso recorder. The blood pressures ranged between 200/130 and 320/150 at the time of injury. In two of these animals, dogs A and C, both the anterior and posterior defects were large and longitudinal in nature. The longitudinal component was again present in the posterior defects of the other 2 animals; however, the anterior defects were stellate. The extent of injury and longitudinal splitting of the hypertensive vessel wall is in direct contrast to the small stellate defects noted consistently in the normotensive vessels injured under the same conditions. The aortic wound of dog A is shown in Figure 7a and b.

Group IV (Table VII). Sixteen dogs were shot in the aorta with either .22 caliber short or long rifle missiles. The defects were usually in the form of small anterior and posterior stellate holes comparable in size to those observed in group II. The margins of the defects had finely ragged edges. Five of the injuries were tangential nicks of the edge of the vessel. One aorta (dog A-71) was com-

TABLE VII.—DATA FROM GROUP IV DOGS (NORMOTENSIVE WITH AORTA EXPOSED TO SALINE)

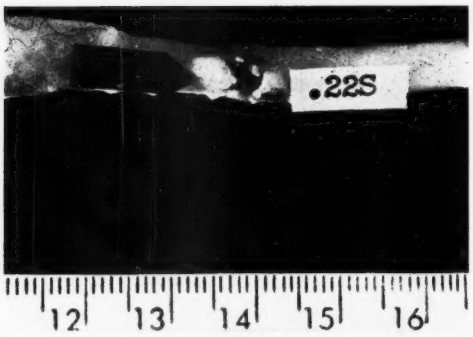
Dog No.	Site of aortic injury	Missile	Size of defects, centimeters	Comment
6	Thoracic	.22 short	ant.: 0.4, post.: 0.4 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-63	Thoracic	.22 short	ant.: 0.8, post.: 0.6 External	Small anterior and posterior stellate defects; intimal damage more extensive
H*	Thoracic	.22 long rifle	ant.: 0.3, post.: 0.2 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-86	Thoracic	.22 short	ant.: 0.6, post.: 0.5 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-83	Thoracic	.22 long rifle	ant.: 0.4, post.: 0.2 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-16	Thoracic	.22 short	No measurements	Small anterior and posterior stellate defects; intimal damage more extensive
E-79	Thoracic	.22 short	ant.: 1.05, post.: 1.05 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-21	Thoracic	.22 short	1.3	Tangential nick; intimal damage more extensive
A-64	Thoracic	.22 short	ant.: 0.8, post.: 1.0 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-71	Thoracic	.22 long rifle	Complete severance (only 0.85 cm. in diameter before injury)	Edges finely ragged
A-65	Abdominal	.22 long rifle	1.5	Tangential nick; intimal damage more extensive
A-68	Abdominal	.22 long rifle	0.85	Tangential nick; intimal damage more extensive
A-70	Thoracic	.22 long rifle	ant.: 1.1, post.: 0.8 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-80	Thoracic	.22 long rifle	1.8	Tangential nick; intimal damage more extensive
A-81	Thoracic	.22 long rifle	ant.: 0.8, post.: 0.7 External	Small anterior and posterior stellate defects; intimal damage more extensive
A-87	Thoracic	.22 short	1.2	Tangential nick; intimal damage more extensive

*See Figure 8a and b.

pletely severed by the missile. In all instances the gross intimal damage was greater than adventitial damage. There was no noticeable difference in extent of injury between those wounds caused by the .22 caliber short and those caused by the .22 caliber long rifle. The aortic wound of dog H, which had a typical injury for this group, is shown in Figure 8a and b.

Group V (Table VIII). In this group, attempts were made to shoot .22 caliber short missiles through the aortas of 5 intact animals. In each instance a long needle was inserted into the thoracic aorta percutaneously and the rifle was sighted in line with the long axis of the needle. The aorta was hit in only 2 of the animals (Table VIII). In intact dog 1 there was great difficulty in placing the needle into the aorta, and it is quite possible that this animal had a pneumothorax at the time of injury. Evidence for this lies in the observation that this injury is similar in nature and extent to the wounds of group I. On the other hand, in intact dog 5 there was no difficulty in placing the aortic needle and there was little possibility of a pneumothorax. This injury is similar in nature and extent to those seen in group IV (Fig. 9a and b). In each instance the intimal damage was greater than that observed externally.

Microscopic examination. The injured aortas of most of the dogs in each of the preceding groups were examined microscopically. Microscopic damage was apparent as fragmentation of the vessel wall, particularly the elastic fibers. The significant feature in all of these injuries, regardless of gross extent, is that in no instance did microscopic injury



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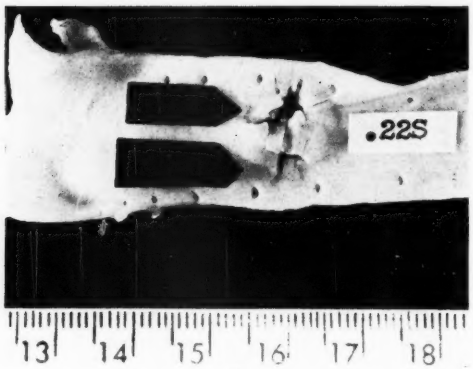

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Fig. 9. Photograph of group V injury of dog intact 5 (see Table VIII). Normotensive thoracic aorta injured when exposed to tissue. Intimal damage is greater than external damage. a, External view of anterior wound. b, Internal view. Anterior defect at upper arrow.

extend farther than 3 millimeters beyond the gross wound.

Débridement and repair. The site of injury, type of missile, occlusion time, and fate of repair are given for each animal in this portion of the study in Tables IX through XIII. The characteristic findings in each group will be given as follows:

Group VI (Table IX). Five dogs are included in this group, one having been injured with a .177 caliber missile and the other 4 with .22 caliber short or long rifle missiles. Occlusion time was measured in only 2 instances and averaged 21.5 minutes. Three of the repairs were initially unsuccessful because the fragmented tissue adjacent to the defects would not hold sutures. Two initially successful repairs became unsatisfactory in 1 and 7 days respectively because of thrombosis at the site of repair. Figure 10a and b shows the thrombosed repair of dog A-68. Figure 11a and b is a photomicrograph of the attempted repair in dog A-21 and shows fragmentation at the site of injury.

Group VII (Table X). Five dogs were studied in this group, and all were injured with .177 caliber missiles. Occlusion time averaged 12 minutes in the 3 instances in which such measurement was made (excluding dog A-16 because part of the occlusion time was spent in taking photographs of the injury). At each repair by longitudinal closure the aorta was narrowed by the defect closure. Two dogs survived to the time of sacrifice at 134 and 76 days respectively. Another repair ruptured on the 26th day. Another dog died on the 17th day of empyema, but some of the sutures of the repair had pulled through the tissue. One dog died just after repair because of difficulty with the mechanical respirator.

TABLE VIII.—DATA FROM GROUP V DOGS (NORMOTENSIVE WITH AORTA EXPOSED TO TISSUE) INJURY TO THORACIC AORTA

Dog No.	Size of defects, centimeters		Comment
Intact 1	ant.: 2.4 post.: 1.5	External	Splitting anterior and posterior injury; probable pneumothorax at time of injury
Intact 5*	ant.: 1.5 post.: 0.8	External	Small anterior and posterior stellate defects; intimal damage more extensive. No pneumothorax

A .22 caliber short missile was used in both these experiments.
*See Figure 9a and b.

TABLE IX.—DATA FROM GROUP VI DOGS (NO DÉBRIDEMENT, TRANSVERSE SUTURE)

Dog No.	Site of aortic injury	Missile	Occlusion time, minutes	Comment
E-79	Thoracic	.22 short	—	Tissue would not hold sutures; unsuccessful
A-21**	Thoracic	.22 short	—	Tissue would not hold sutures; unsuccessful
A-68*	Abdominal	.22 long rifle	15	Thrombosis and death in 24 hours
6	Thoracic	.22 short	—	Tissue would not hold sutures; unsuccessful
A-12	Abdominal	.177	28	Thrombosis and death in 7 days (gangrene hind legs)

*See Figure 10a and b.
**See Figure 11a and b.

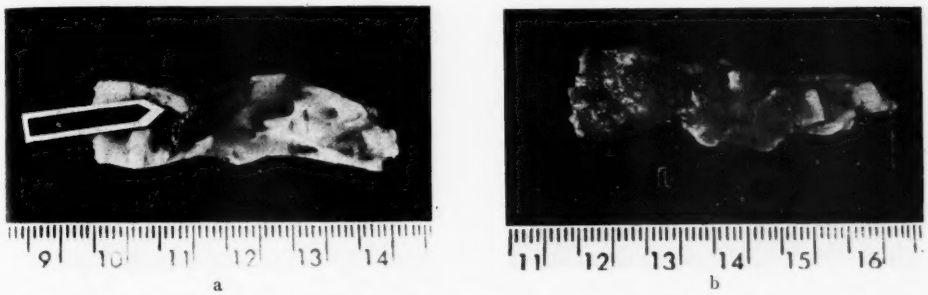


Fig. 10. Group VI repair of dog A-68 (see Table IX). Abdominal aorta injured with .22 caliber long rifle missile. Repaired with no débridement and transverse suture. a, Internal view showing thrombus. b, External view.

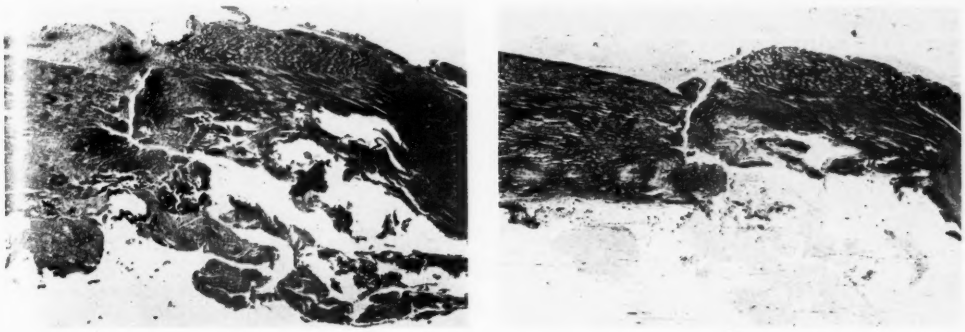


Fig. 11. Photomicrograph of group VI repair of dog A-21 (see Table IX). The intimal side is up. Note excessive fragmentation of the wall. a, Hematoxylin and eosin stain. b, Weigert's elastic tissue stain. ×23.

Group VIII (*Table XI*). Both dogs in this group were injured with .177 caliber missiles. The average occlusion time was 15 minutes. Both repairs were satisfactory from the standpoint of function although each was narrowed at the site of repair. Figure 12 shows the specimen from dog A-21 at the time of sacrifice inflated to 120 millimeters of mercury pressure with air.

Group IX (*Table XII*). All 6 dogs in this group were shot with one of the .22 caliber missiles. The average occlusion time was 13 minutes. In each instance the aortic wall held the sutures well, but there was either angulation or irregularity at the suture line. In spite of this undesirable distortion of vessel alignment, all the repairs functioned satisfactorily until sacrifice, excluding that in dog A-16. In this animal thrombosis and death occurred on the 16th day and was probably related to

TABLE X.—DATA FROM GROUP VII DOGS (NO DÉBRIDEMENT, LONGITUDINAL SUTURE)

Dog No.	Site of aortic injury	Occlusion time, minutes	Comment
A-16	Abdominal	30 (photographs taken)	Diameter narrowed from 1.0 to 0.75 cm. at repair. For 134 days repair functioned, then sacrifice
A-11	Abdominal	14	Diameter narrowed from 0.95 to 0.80 cm. at repair. For 76 days repair functioned, then sacrifice
E-98	Thoracic	8	Site of repair ruptured on 26th day, empyema, aorta originally somewhat sclerotic, narrowed from 1.6 to 1.3 cm.
1	Thoracic	—	Died during chest wall closure of anesthesia difficulty; intimal damage noted to extend beyond repair; narrowed slightly at repair
A-35	Thoracic	13	Diameter narrowed from 1.4 to 1.1 cm. at repair; died on 17th day of empyema; repair held, but some sutures had pulled through

A .177 caliber missile was used in all these experiments.

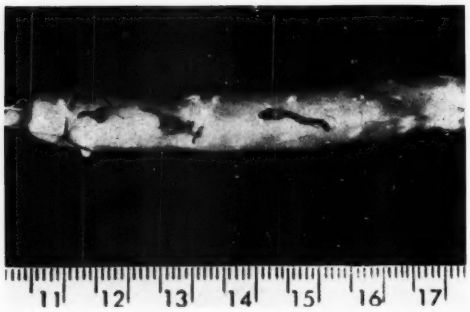


Fig. 12. Photograph of group VIII repair of dog A-21 (see Table XI). Abdominal aorta injured with .177 caliber missile. Repaired with longitudinal suture after débriding the ragged edges. Specimen inflated to 120 millimeters of mercury with air 112 days after repair. Note slight constriction at repair.

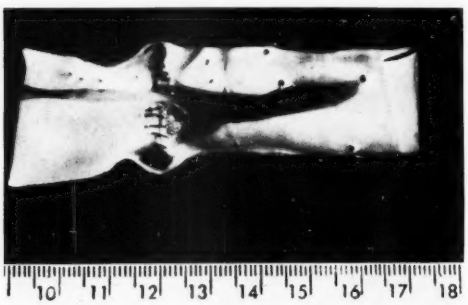


Fig. 13. Photograph of open thoracic aorta from dog dying 16 days after wedge débridement and transverse suture of gunshot wounds resulting from .22 caliber short missile (dog A-16, Group IX, Table XII). Note sacculation at level of repair and thrombus arising from suture line. The angulation of the artery before it was opened was such that the acute angle was on the side of the suture line (side away from the camera).

distortion of blood flow (Fig. 13). Figure 14a and b shows a typical repair in this group (dog A-64). Figure 15 is an aortogram of dog A-65 showing distortion of the line of flow at the site of repair.

Group X (Table XIII). All 6 dogs in this group were injured with either .22 caliber short or long rifle missiles. The average occlusion time was 9.3 minutes. Segments up to 2.0 centimeters were resected. In each instance initial repair was satisfactory and 4 of the dogs survived for 61, 52, 169, and 153 days, respectively, at which times they were sacrificed. One of the dogs (A-83) died 24

TABLE XI.—DATA FROM GROUP VIII DOGS (RAGGED EDGES DÉBRIDED, LONGITUDINAL SUTURE) INJURY TO ABDOMINAL AORTA

Dog No.	Occlusion time, minutes	Comment
E-79	14	Diameter narrowed from 0.7 to 0.55 cm. at repair; repair functioned for 115 days, then sacrifice
A-21*	16	Diameter narrowed from 1.0 to 0.8 cm. at repair; repair functioned for 112 days, then sacrifice

A .177 caliber missile was used in both these experiments.
*See Figure 12.

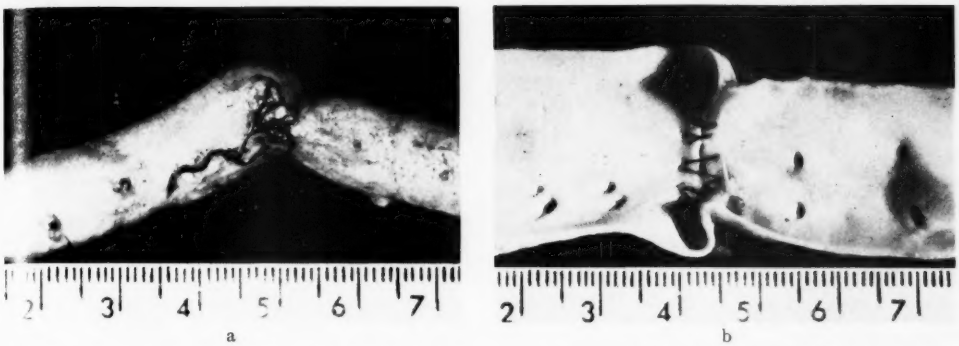
TABLE XII.—DATA FROM GROUP IX DOGS (WEDGE RESECTION, TRANSVERSE SUTURE)

Dog No.	Site of aortic injury	Missile	Occlusion time, minutes	Comment
H	Abdominal	.22 short	12	Angulated at site of repair; function satisfactory for 28 days, then sacrifice
A-16*	Thoracic	.22 short	10.5	Angulated at site of repair; thrombosis and death in 16 days
A-63	Thoracic	.22 short	12.5	Angulated at site of repair; function satisfactory for 32 days, then sacrifice
A-64**	Thoracic	.22 short	14	Angulated at site of repair; function satisfactory for 180 days, then sacrifice
A-65***	Abdominal	.22 long rifle	20	"Dog ears" at site of repair; function satisfactory for 177 days, then sacrifice
A-87	Thoracic	.22 short	11	"Dog ears" at site of repair; function satisfactory for 7 days, then died of empyema

*See Figure 13.
**See Figure 14a and b.
***See Figure 15.

hours after injury because of atelectasis, but the repair was satisfactory. Dog A-70 died in 48 hours, and at autopsy it was noted that the right lung had been perforated by the missile. The aorta was thrombosed at the site of repair, which we attribute to postoperative bleeding and hypotension secondary to the lung perforation. Figure 16a and b shows the specimen from dog A-86, removed at sacrifice on the 153rd postoperative day. Figure 17 shows the aortogram of dog A-86, made just prior to sacrifice. Figure 18a and b is a photomicrograph of the repair site in the same animal at the time of sacrifice (153 days after repair).

Microscopic examination. Almost all of the repairs in this portion of the study were ex-



a b

ig. 14. Photograph of group IX repair of dog A-64 (see T le XII). Note sacculation and angulation at site of repair. Functioned well for 180 days. a, Inflated to 120 millimeters of mercury with air. b, Internal view.

a ined microscopically. Débridement was th ught to have been adequate in groups IX a l X, using the absence of fragmented vessel w ll as a criterion of adequacy. Residual fr gmented aortic wall was noted in groups V . VII, and VIII.

DISCUSSION

Nature and extent of injury. The outstanding observations from this portion of our study are: (1) The resultant injury in normotensive vessels exposed to air was much greater in gross extent than that in normotensive vessels injured while surrounded by saline solution or body tissue. (2) The hypotensive vessels were injured to a much smaller gross extent than were normotensive vessels under the same conditions. (3) The hypertensive vessels tended to split extensively in a longitudinal direction as contrasted with the smaller stellate defects of the normotensive vessel under the same conditions. (4) Regardless of the conditions of injury, extent of intimal damage always exceeded apparent external extent of damage. (5) In no instance in any of the groups studied did microscopic damage extend more than 3 millimeters beyond the gross intimal damage.

An ingenious group of experiments has been reported from Princeton University on the mechanism of wounding by high velocity missiles although no reference was made by these workers specifically to arterial injury (6–9, 22, 24). Through the use of high speed moving pictures, roentgenograms, and instantaneous

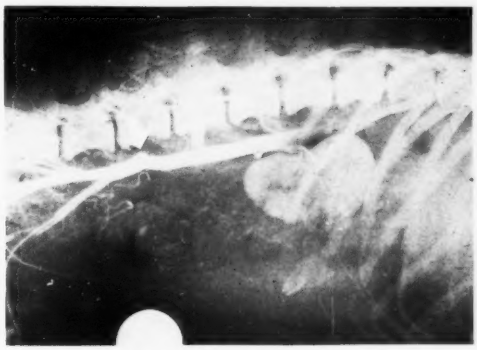
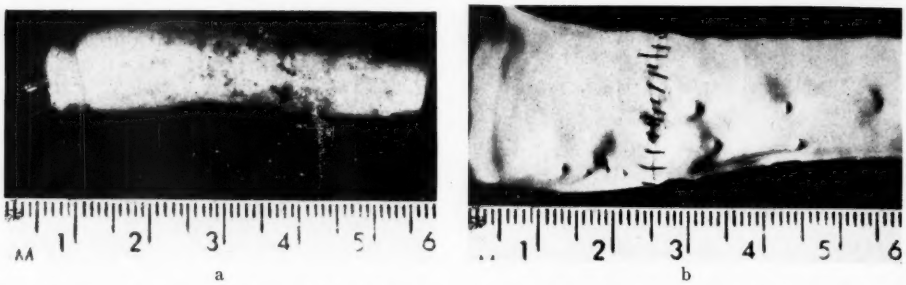


Fig. 15. Aortogram of group IX repair of dog A-65 made 52 days after repair (Table XII). Arrow indicates distortion of line of flow at repair.

spark shadowgrams, these authors were able to elucidate the physical properties of the temporary cavity that always follows in the wake of a high velocity missile. They have shown that the important factor in producing tissue damage is displacement and overstretching of tissues by the missile and by the temporary cavity which follows in the path of the missile. This factor is to be distinguished from the "shock wave" which precedes the missile and which travels with the speed of sound in the tissue. The Princeton group has shown that this "shock wave" produces no tissue displacement and, therefore, is unimportant in producing tissue damage. The energy necessary to displace tissue is derived from the kinetic energy of the advancing projectile through its closely follow-



a b

Fig. 16. Photograph of group X repair of dog A-86 (see Table XIII). Specimen removed on 153rd day after repair. Note excellent alignment. a, Inflated to 120 millimeters of mercury with air. b, Internal view.

ing temporary cavity. The striking energy, E, of a missile can be expressed in the following formula, where m = mass of bullet and v = velocity with which it travels:

$$E = \frac{mv^2}{2}$$ (Smith and Glaister, 1939)

These observations by the Princeton group can be applied to our experiments on arterial gunshot wounds. Figure 19 is a diagrammatic representation of the "shock wave" produced as the missile strikes the artery. This "shock wave" is of no importance in blood vessel injury as it causes no displacement and overstretching of the arterial wall. The mere penetration of the arterial walls by the bullet does cause displacement of tissue and overstretching of the walls sufficient to cause damage. This factor is represented in Figure 20. Large injuries were obtained when normotensive vessels were exposed to air at the time of wounding. The temporary cavity causes displacement of the arterial walls with overstretching of tissue, thereby causing damage (Fig. 21). When normotensive arteries were surrounded by saline solution or normal body tissue, the injuries were small. This is due to equalization of energy on both sides of the vessel wall. The temporary cavity exerts its distorting pressure via the saline or tissue and tends to displace the wall inward, while the cavity within the vessel tends to displace the wall outward. These two opposite forces cancel each other to some extent and minimize the resultant damage (Fig. 22). It is probably because of this cancellation of opposite forces that we could note no appreciable difference in extent of injury between the two .22 caliber missiles. Of course, the difference in diameter between the .177 and the .22 caliber projectiles would account for some difference in size of defects in these 2 instances.

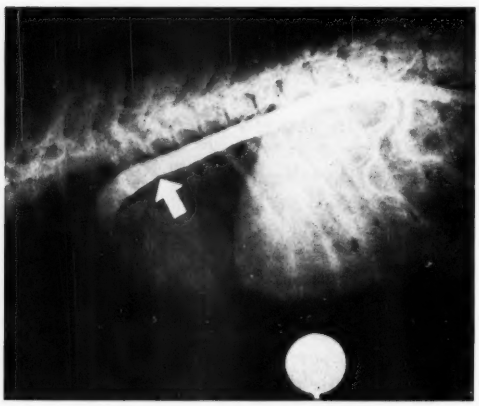
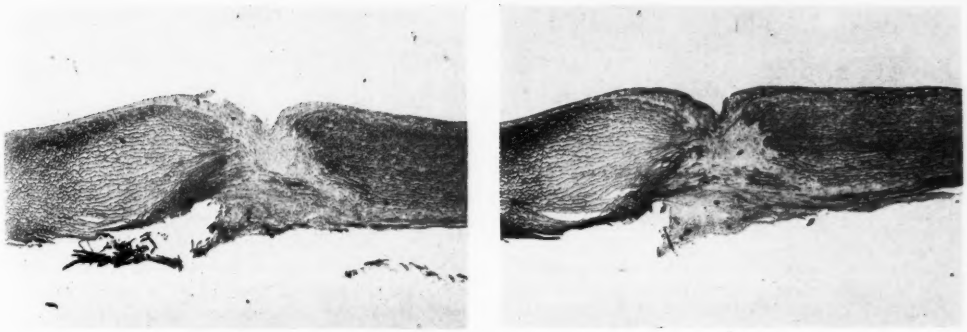


Fig. 17. Aortogram of group X repair of dog A-86 (see Table XIII). Note excellent alignment at repair indicated by arrow. Aortogram was made on 153rd day after repair.

With reference to the small injuries obtained in the hypotensive vessels, the following explanation is offered: When hypotension exists, the vessel walls are relatively flaccid and, therefore, are capable of greater displacement without damage. In other words, the *tensile tolerance* of the arterial wall must be exceeded before anatomic damage can occur.

The implications of excessive intimal damage and small excess of microscopic over gross injury will be discussed.

Summarily, it may be stated that the extent of gunshot injury of arteries depends upon



a b

Fig. 18. Photomicrograph of group X repair of dog A-86 (see Table XIII). Intimal side is up. Note excellent healing. Suture line is at intimal depression. a, Hematoxylin and eosin stain. b, Weigert's elastic tissue stain. ×23.

two main factors: (1) the projection area of the missile that perforates the wall, and (2) the degree to which displacement of the wall exceeds the tensile tolerance of the vessel wall. Regarding the latter factor, we would expect the hypertensive or sclerotic vessel to be damaged more extensively than the normal vessel. In the case of the hypertensive artery, its walls are already displaced by the increased pressure from within. Therefore, a smaller than normal increment of pressure would displace the walls beyond the limits of tensile tolerance and the extent of injury should be greater than in the instance of the normotensive vessel. This expectation was borne out in our group III experiments. The sclerotic vessel, of course, has a low tensile tolerance to begin with and only minimal displacement would produce anatomic damage.

Débridement and repair. As far as necessary extent of débridement is concerned, one has only to be certain that all microscopically fragmented tissue is removed. Under the conditions of our experiment microscopic damage was *not* observed farther than 3 millimeters from the gross wound margin. It should be emphasized that this rule of 3 millimeters applies to the *internal* gross defect, which is itself apt to be more extensive than the external gross defect. To débride only 3 millimeters beyond the *external* gross defect is not enough. Therefore, any débridement that extends for at least this distance on all sides of the gross internal defect should be adequate in arterial wounds caused by these missiles.

It should be emphasized that the gross extent of injury should be judged on the basis of intimal as well as external inspection. A nerve hook is useful for gently retracting the arterial walls to allow internal inspection.

Adequate débridement was achieved in our experiments by excising a wedge of injured wall. However, the resultant distortion of blood flow is an undesirable characteristic of repair preceded by this type of débridement.

TABLE XIII.—DATA FROM GROUP X DOGS (RESECT SEGMENT, ANASTOMOSIS) INJURY TO THORACIC AORTA

Dog No.	Occlusion time, minutes	Comment
A-71	10	0.6 cm. resected; functioned well until sacrifice on 61st day
A-80	8	2.7 cm. resected; functioned well until sacrifice on 52nd day
A-81	11	1.5 cm. resected; functioned well until sacrifice on 169th day
A-86*	9	2.0 cm. resected; functioned well until sacrifice on 153rd day
A-70	8.8	1.5 cm. resected; thrombosis and death in 48 hours; unrecognized injury to opposite lung with bleeding; hypotension probably contributed to thrombosis
A-83	9	2.0 cm. resected; died 24 hours of atelectasis, right lung; repair satisfactory

A .22 caliber long rifle missile was used in all these experiments except Dog A-86 where a .22 short missile was utilized.
*See Figure 16a and b, Figure 17, and Figure 18a and b.

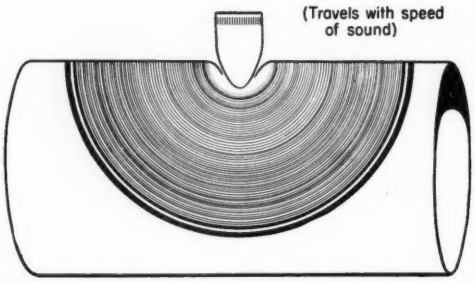


Fig. 19. Diagrammatic representation of "shock wave" (unimportant in blood vessel injury).

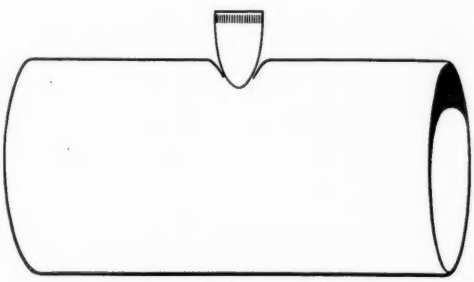


Fig. 20. Diagram of arterial wall being perforated by missile (see text).

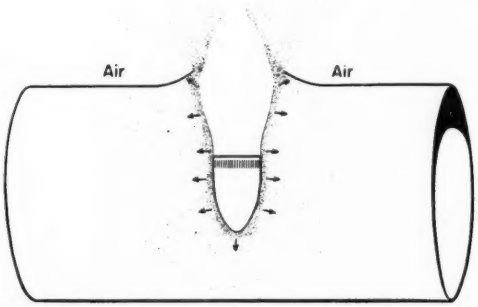


Fig. 21. Diagram showing unopposed displacement of wall by cavity and transmitted energy when vessel is exposed to air. Small arrows indicate force (see text).

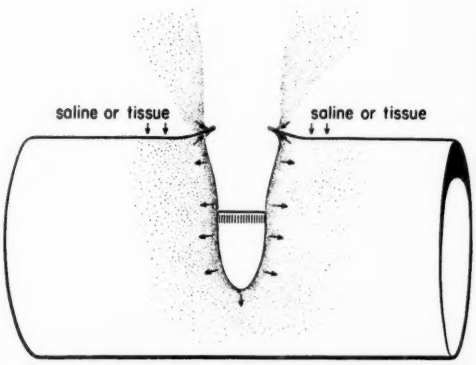


Fig. 22. Diagram showing opposing forces (indicated by arrows) when vessel is exposed to saline or other tissue, which tend to minimize vessel wall displacement (see text).

We are of the opinion that resection of the entire injured length of vessel followed by end-to-end anastomosis gives the most satisfactory results with least disturbance of blood flow. Another advantage of this method is that it can be done with a shorter occlusion time.

Longitudinal closure of a defect always results in some narrowing of the vessel and is, therefore, undesirable.

It should be kept in mind that when gunshot wounds of arteries are explored, hemostasis can quickly be achieved by digital pressure over the defects while adjacent portions of the vessel are being freed. In this manner, occlusion of flow through the vessel will not be interrupted until one is ready to perform the débridement and definitive repair.

Finally, we would like to suggest that if a large length of vessel must be sacrificed for the sake of adequate débridement, a vascular graft may be utilized, if available. This should rarely be necessary in cases of injury due to the missiles studied in this work.

General considerations. By way of final discussion, we would like to emphasize two points: (1) Many patients with gunshot wounds of arteries, even of the aorta, *do* survive long enough to reach surgical care. (2) The principles which we have derived from this work can be applied to gunshot wounds of any major artery, although in our experiments we used only the aorta of dogs for reasons discussed.

SUMMARY

1. The feasibility of repairing gunshot wounds of major arteries is emphasized.

2. A personal case of gunshot wound of the abdominal aorta is presented in detail.

3. An experimental study of gunshot wounds of the aorta of dogs is presented. Some general principles regarding nature and extent of injury and methods of débridement and repair are defined on the basis of our study.

CONCLUSIONS

1. There are enough available published reports to indicate that many patients with gunshot wounds of major arteries—even of the aorta—can survive long enough to reach surgical care.

2. The resultant defects produced by gunshot injuries of major arteries depend upon two main factors: (1) the projection area of the missile that perforates the arterial wall, and (2) the degree to which displacement of the wall exceeds the tensile tolerance of the vessel wall.

3. Gross intimal damage usually exceeds apparent external damage in extent.

4. Microscopic damage usually extends no farther than 3 millimeters beyond the gross intimal damage. Consequently, under the conditions of our experiments, adequate débridement can be achieved by excising no more than 3 millimeters of tissue beyond the gross intimal defect.

5. Longitudinal closure of arterial defects after débridement almost always leads to undesirable narrowing of the lumen.

6. Transverse closure after partial circumferential excision of the wall almost always results in distortion of the line of blood flow. The latter may cause thrombosis at the site of repair.

7. The optimal method of débridement and repair is resection of the injured segment at least 3 millimeters beyond the gross intimal defect, followed by axial anastomosis.

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BIOLOGIC PREDETERMINISM IN GASTRIC CARCINOMA AS THE LIMITING FACTOR OF CURABILITY

IAN MACDONALD, M.D., F.A.C.S., and PAUL KOTIN, M.D., Los Angeles, California

IN A GENERAL discussion of biologic predeterminism in human cancer one of us (I.M.) presented evidence from several sources showing that both resectability and curability of gastric carcinoma increased in proportion to the duration of symptoms of the disease. The concept that early diagnosis of carcinoma of the stomach may improve end results is not only fallacious but is in fact the reverse of the truth. Patients with progressively longer periods of delay, from onset of symptoms to the time of exploration, enjoy increasingly better chances of resection and long term survival. In a review of 375 cases of gastric carcinoma, Swynnerton and Truelove noted that "an outstanding finding of the present study is the marked prognostic significance of length of history among patients treated with surgical resection. The greater the length of history the better the prognosis." Repeated observations of this seeming paradox direct attention to the need for identifying factors other than early diagnosis as the avenues through which survival rates in gastric carcinoma might be improved, if this is possible with present techniques.

This is a study of factors inherent in natural selection, or biologic predeterminism, acting as indicators of less lethal patterns of neoplastic growth. Lesions which long remain confined to the gastric pouch and perigastric nodes produce slowly developing symptoms of gastric dysfunction over long intervals of time. The obverse of this more favorable pattern is that represented by about 40 per cent of patients in whom a high growth potential produces a rapidly developing clinical reflection of the general effects of local and metastatic spread as early manifestations. This group presents little or no symptomatology of gastric dysfunction, and such patients usually die with the primary lesion undiagnosed. The most lethal pattern of gastric carcinoma is thus one in which the patient never has a chance to temporize, for as far as the primary site of the lesion is concerned the traditional signals of danger never become manifest. The "earliest" symptoms thus bespeak incurability, and the patient may come to autopsy with a completely occult primary lesion in which there has been zero delay clinically. Between these two extremes of biologic behavior are gradations of patterns in local growth, regional spread, and distant dissemination, and it becomes apparent that natural selection, rather than the type or time of treatment, determines resectability and curability in this disease.

If this concept of biologic predeterminism is valid, then the present emphasis on "early" symptoms of gastric cancer is so much blind furor against an as yet unacknowledged barrier of biologic inevitability. For much the same reason, one may question the value of a more general application of total gastrectomy as advocated by some surgeons in recent years.

With this in mind it seems timely, then, to examine the validity of the popular exhortation in current surgical literature concerning the need for "early" diagnosis and more radical extirpative efforts. Evidence is readily available from accumulated information which clearly outlines the natural history of gastric carcinoma, which evidence is manifestly universal even though its implications are overlooked by many authors. Raffl and Kelley refer to the appalling delay in cases reviewed by them in whom "the average duration of symptoms before entering the hospital was: overall, 8.5 months; inoperable, 9.0 months; explored, 6.8 months; received surgical palliation, 7.7 months; resected, 9.0 months." As is immediately apparent, the resected group has a longer symptom duration interval than all others except the inoperable group which

From the Departments of Surgery and Pathology, School of Medicine, University of Southern California and the Los Angeles County Hospital.

for all purposes it equals. Data from three general sources of evidence are pertinent. (1) The local regional and distal spread of the disease during life, (2) the ultimate patterns of spread observed at autopsy, and (3) the end results following definitive surgical treatment.

Gastric carcinoma exhibits an extraordinary diversity in its pattern of growth and dissemination. Variations in morphology are represented by the special undifferentiated carcinoma or "blue cell cancer" of Steiner, mucinous carcinoma, infiltrating scirrhous carcinoma, and undifferentiated anaplastic carcinoma.

In the analysis of 1,467 cases of gastric carcinoma at the Los Angeles County Hospital, the best prognosis was associated with the adenocarcinoma and blue cell type, and the poorest with the mucinous, infiltrating scirrhous, and anaplastic. A future report will detail the relationships and associations between histopathologic pattern and biologic behavior of gastric carcinoma.

The primary lesion may spread in luminal fashion through the mucosa, or transmurally, either in focal areas or en bloc to involve the serosa, or, finally, by extension to the adjacent structures. Intramural extension is usually ominous, and cancerization of the mucosa far beyond the limits of visible or palpable involvements is almost invariable. Eker has seen microscopic extensions 5 centimeters beyond the apparent margin of the tumor, a finding confirmed by others. This finding relates directly to prognosis as reported by Steiner and others. Steiner used the degree of circumscription of the tumor determined microscopically, as a reliable indication of prognosis. Widespread mural extension may be, in the instance of the more distal lesions, either on the cardiac or duodenal side of the resection. Lesions of the cardia are almost uniformly unfavorable in this respect, Brownson having demonstrated microscopic infiltration of the esophagus in 26 of 27 specimens. These are the findings usually recited by the advocates of routine total gastrectomy, when in fact such a pattern of spread is evidence of biologic incurability.

There is ample proof that widespread mural extension, rather than being an argument for more radical surgery, is an indication that no feasible extension of the operative procedure will encompass the neoplasm. Harvey and associates in a study of 453 resections found no evidence that a wide margin beyond the neoplasm was of any importance. In 18 of their 60 five year survivors with clinical control, an excisional margin of less than 2 centimeters was noted, while in 3 of these clinical "cures" resection actually was done through the cancer. Thomas and his co-workers, in reviewing 147 cancers of the stomach, commented: "The question of total gastrectomy for all gastric cancers is a provocative one. It should not be decided, however, on grounds of dissatisfaction with present modes of treatment. It must be decided on its merits pathologically and on its end results in terms of years of life . . . the one series based on this concept has given most disappointing results."

In a study of local recurrences based on 92 autopsies, McNeer and his associates reported that when less than half of the stomach had been removed 64 per cent developed local recurrence, while with progressively wider resection of the gastric pouch local recurrence was present in 79, 74, and 67 per cent, again indicating that the width of mural resection is of no determinative importance. In 133 resection survivors reported by Guiss all of the 5 year cures were obtained by subtotal gastrectomy. Ransom, in a review of 457 cases in which definitive surgical procedures were carried out, studied 55 deaths with reference to residual neoplasm, and he concluded that "in only 3 was there evidence that a total gastrectomy instead of a subtotal resection performed, might have given a better result."

Serosal involvement and extension to other structures may appear more formidable than intramural extension yet both may be consistent with curability. Pack and McNeer (15) report 50 per cent 5 year cures in 16 patients with serosal extension. About one-third of all cases have evidence of a predilection for regional extension rather than metastasis, and such patients may become eligible for cure by wide omental resection and splenectomy. The fundal lesions are an exception, for nearly all of them infiltrate the diaphragm as well as the esophageal wall, and

nearly all of the proximal lesions metastasize before any symptoms indicate their presence.

The pattern of lymphatic spread is a further obstacle to the application of adequate surgical measures for gastric cancer, a limiting factor to which little attention has been paid. Even with total or near-total gastrectomy and wide resection of omenta combined with splenectomy, the extirpation of regional lymphatics thus accomplished is not comparable to that achieved in lesions of the colon. The immediate perigastric nodes are but the first zone of regional lymphatic spread and analogous, perhaps, to the nodes in the lower third of the axilla to which mammary carcinoma first disseminates. Of the secondary nodal areas, the least important but most readily accessible is the pancreaticolienal, removal of which is secured by concomitant splenectomy. There remain the hepatic and subpyloric nodes, the relations of which to the duodenum and pancreatic head are such as to require resection of these viscera to secure a really radical lymphadenectomy. More often than not the presence of metastases in these lymph nodes is an indication of further extension to the celiac axis group of para-aortic nodes, and more frequently the presence of such lymphatic extension is a signal of more remote metastases, hepatic or other. Both from technical and biologic viewpoints, gastric cancer is at present a surgically insoluble problem. Even if the theoretically desirable radical procedure of total gastrectomy with splenectomy and pancreaticoduodenectomy were practicable, its justification by the frequent demonstration of metastases in the additional lymph nodes thus dissected would only emphasize the futility of such superradicalism.

With a genuine subtotal, as distinct from a partial, gastrectomy and wide omental resection, both the presence of nodal metastases and the number of nodes so involved are significant. Pack and McNeer report 42 per cent 5 year survivals without, and 24 per cent with, nodal metastases. Harvey and his group reported that only 20 of 60 five year survivors had nodal metastases, and of these only 4 had 3 or more nodes involved.

Autopsy findings in postresection cases verify these observations concerning local growth and regional spread of gastric cancer, although again some authors fail to derive conclusions which seem obvious to us. Failure of local control is lamented by McNeer and his associates, Berne and Freedman, and Friesen, though they fail to prove that gastric or duodenal recurrence was not accompanied either by distant metastases or by regional spread usually beyond technical operability. The fact that 80 per cent or more of postresection autopsies show failure of local control can most logically be explained as evidence that this major fraction is biologically uncontrollable, leaving about 20 per cent in which the local disease may be surgically encompassed.

Except for diffuse gastric infiltration, the surgeon's ability to control local recurrence has little to do with the size of the primary lesion. McNeer's autopsy review showed that for lesions measuring less than 3 centimeters, 3 to 5 centimeters, and more than 5 centimeters, local recurrence rates were, respectively, 63, 68, and 75 per cent. Ochsner and Blalock, in reviewing the necessity for the re-evaluation of therapeutic philosophy in carcinoma of the stomach, observed in a review of 210 cases of gastric carcinoma, "this study shows, however, that radical subtotal gastrectomy, when it can be done, gives excellent results." Surgical heroism was appropriately commented upon by Boyce in a review of 200 cases of carcinoma of the stomach, 11 of whom were subjected to total gastrectomy, even though the procedure was without curative promise for any of them. He observed: "These cases in fact prove again that in this disease the stage and location of the growth, not the skill and ability of the surgeon, determine the end result of the individual case." Ochsner and Blalock and Boyce offer abundant evidence of predeterminism in gastric cancer, in spite of the diagnostic interval, though concluding with an emphasis on the importance of "early" diagnosis. The former authors comment "that to increase the 5 year survival rate in gastric cancer the patient must be treated when the disease cannot be diagnosed i.e., as gastric carcinoma." This is an admission that the inexorable course of individual cases is determined at the onset of neoplasia.

A further implication is, in our opinion, the utility of mass methods of screening asymptomatic individuals for gastric cancer, either by radiographic or cytologic technique. Chief barriers, of course, are those imposed by the psychology of the average citizen and the utterly insoluble problem of trained personnel for mass screening at sufficiently frequent intervals. More basic, however, is the evidence that, in general, predeterminism is established at the inceptive phase of neoplasia, before the disease can be detected by any screening technique at present available. This is not to say that prompt efforts directed toward diagnosis and treatment in the patient with symptoms are not commendable. It seems apparent, however, that any combination of screening and early diagnosis, and reduction of delay from diagnosis to treatment, will produce no more than a minor, fractional improvement in end results. In short, present methods of management, under ideal conditions, are producing the best present feasible control. The evidence presented here suggests that under utopian conditions of diagnosis and treatment, less than 20 per cent of all gastric carcinoma is controllable for 5 years or more.

Most convincing of all evidence as to biologic predeterminism in gastric carcinoma is the failure of the disease to yield in the face of rising rates of operability and resectability. In a semi-inspirational article in the journal *CA*, Pack (14) states that curability had increased 400 per cent in 12 years, and so it had, in from about 3 to 12 per cent of all cases. But the resectability rate had increased from 2.9 to 39 per cent, or some 1,300 per cent, while the mortality following subtotal gastrectomy had decreased from 62 to 9.8 per cent. With more realism, Harvey and his associates report an increase in resectability to 43 per cent from 28 per cent overall average, but with a decrease in 4 year survivors from 14 to 12.4 per cent. State, Moore, and Wangensteen in 1945 reported 80 per cent resectability, and only 4.9 per cent mortality, representing a net percentage gain of 72 per cent in resection survivors since 1936, yet their last available overall 5 year results were only 6.6 per cent. Similarly, Jemerin and Colp report a net gain in resection survivors of 19 per cent from 1938 to 1947, but only 3.5 per cent increase in resection survivals for 5 years.

Further proof of the failure of early diagnosis to improve curability is reported by Jemerin and Colp, with the best indications for resection being found after duration of symptoms of from 6 to 12 months.

Anderson, Dockerty, and Gray in 100 cases resected for malignant pyloric obstruction found that 70 per cent of the 5 year survivors, but only 34 per cent of the entire group, had symptoms for more than 2 years.

A better perspective as well as a more accurate index of the inexorable biology of gastric cancer is obtained by comparing two widely separated eras in American surgery. The earliest large series of cases is that reported by C. W. Mayo for the years 1897 to 1919, during which 2,094 operations were done for gastric cancer, of which 736 or 35 per cent were resections. Comparable figures for these subtotal resections, and the same procedure as done by Pack and his group from 1942 to 1946, 35 years later, when 39.8 of all cases were resectable, are: resection mortality, Mayo, 13.7 per cent and Pack, 9.8 per cent; net 5 year cure rate, Mayo, 25 per cent and Pack, 35 per cent. The net progress of 35 years is thus 4 per cent decrease in resection mortality and a 10 per cent gain in 5 year resection survivors.

Some consideration must be given to the fact that most of the end results quoted in the foregoing are from specialized institutions and services and are not representative of the total picture of gastric cancer in the general population. The latter is more accurately reflected by surveying a true cross section of the disease in an area, as Guiss did with a series of 2,891 cases. In this study the 5 year survival for all cases was 1.4 per cent, but for recent years the resectability rate was 28 per cent for private hospitals and 7 per cent for the medically indigent. This is probably a true reflection of the value of early diagnosis, i.e., a fourfold difference in resectability. There is no such difference in end results, for the 5 year survivors of resection were statistically identical for the private and indigent cases, at 33 and 31 per cent respectively. Assuming, as seems proper, that earlier exploration would increase

resectability by 21 per cent, and that one-third of this group would join the 5 year survivors, the overall end result reported by Guiss might rise to almost 9 per cent, approaching the 12 per cent figure from specialized centers which tend to draw patients with a more favorable type of disease than those seen in community hospitals.

Only one further phase of the effort toward resection at an earlier stage of the disease is promising. This is in the much debated situation in which a gastric ulcer is demonstrated, and radiographic or other evidence fails to indicate a neoplastic lesion. Particularly in patients past 40 years of age, prompt resort to resection will undoubtedly achieve extirpation of a few gastric carcinomas which are still limited to the viscus. Medical treatment of such ulcers should be limited to a period of several weeks, and the surgical procedure should be of the same extent as for a recognized neoplasm.

CONCLUSIONS

1. Biologic predeterminism, rather than the time or type of surgical treatment, governs end results in gastric carcinoma.

2. Natural selection is the best indicator of operability and possible resectability. In general, patients with well defined symptoms of gastric dysfunction are the best surgical candidates.

3. Duration of symptoms bears some relation to resectability, but curability increases with duration of symptoms in resectable cases.

4. The mechanism of mural and regional spread is such that total gastrectomy offers no promise of increase in curability.

5. The only genuine "early" treatment is gastric resection for gastric ulcer which may be carcinoma.

6. Radical, extended surgery will be curative for some locally extensive lesions infiltrating adjacent structures, without evidence of remote metastases.

7. Present evidence indicates that, under the most ideal circumstances, less than 20 per cent of all gastric cancer is surgically curable.

8. Increase in resectability rates above the level of 40 per cent may be of palliative value but, beyond that point, reaches an area of diminishing returns as to relative 5 year cures.

9. The most satisfactory procedure, by criteria of curative and physiologic end results, is genuine subtotal gastrectomy with wide omental resection and splenectomy.

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THE COMBINED COOPER'S LIGAMENT AND INGUINAL LIGAMENT HERNIA REPAIR

CLAUD C. BURTON, M.D., F.A.C.S., Dayton, Ohio

THERE is much to commend the growing tendency of surgeons to simplify the classification of hernia operations by placing them in two major categories: inguinal ligament hernia repair and Cooper's ligament hernia repair. Although generally recognized as separate and distinct operative procedures, they are, nevertheless, closely related anatomically, clinically, and in their expectancy of a secure wall. The two major operative procedures have numerous variants, yet, significantly and inexplicably they have never truly become integrated. It is reasonable to assume that a much stronger wall would accrue if an integration of the two repairs could be achieved.

It is our conviction that the intermediary link to the integration of inguinal ligament and Cooper's ligament repairs has been discovered. If the proposed reparative variant for overcoming the long existent anatomic barrier is as effective as it appears from observing a representative series of cases, it means a significantly progressive step has been taken toward greater and more uniform security of the wall. In such an analysis, the triple role of the inguinal ligament; (a) its pectinealization, (b) its bridging of the interligamentous space, and (c) its synthesis with the pectinealized parietal wall in the combined maneuver of Cooper's ligament repair should be re-emphasized.

Based upon the experience in this clinic with the combined or integrating maneuver, it is believed that the results warrant a discussion of the composite Cooper's ligament repair in terms of three distinct maneuvers: *parietopectineal*, or first maneuver; *inguinopectineal*, or second maneuver; and the proposed *combined*, or third maneuver.

From the Veterans Administration Center, Dayton, Ohio, and the Department of Surgery, University of Cincinnati College of Medicine.

The discussion of the proposed technical steps is prefaced by some pertinent remarks on the trihedral space as it relates to the combined operation. The spermatic canal is divided into the inguinal canal and the scrotal canal (Fig. 1A). With careful anatomic observations as regards the dynamics of the inguinal canal, made at the time of operation, there has come the realization that the normal inguinal canal, which has not become distorted by intracanalicular or intra-abdominal pressure, is a trihedral space in contrast to the cylindrical scrotal canal. The boundaries of the trihedral space which contains the inguinal canal are: inferiorly, the anterior inguinal and intermediate iliopubic ligaments and the interligamentous space with its intervening pectineal fascia; posteriorly, Cooper's ligament and the fascia transversalis; and, anteriorly, the external oblique aponeurosis, internal oblique and transversus abdominis muscles (Fig. 1B). These structural boundaries retain their mural characteristics in the form of three distinct trilateral planes which are primarily protective and do not intimately surround the cord with the possible exception of the obliquus internus on contraction of its fascicular portion.

The superolateral or transitional portion of the canal is quite important strategically. It is recognized by its slight cephalad angulation which is more pronounced in Cooper's ligament repairs. It extends from the pectineovascular junction to the abdominal ring. The size of this vulnerable area is dependent upon the hernial protrusion which of course is lateral to the inferior epigastric vessels and, therefore, must fall in the category of indirect hernia. If the protrusion is large, one should always think of a concomitant sliding hernia. The structural relations which obtain in this area and which cause concern in the repair of this portion of the canal are

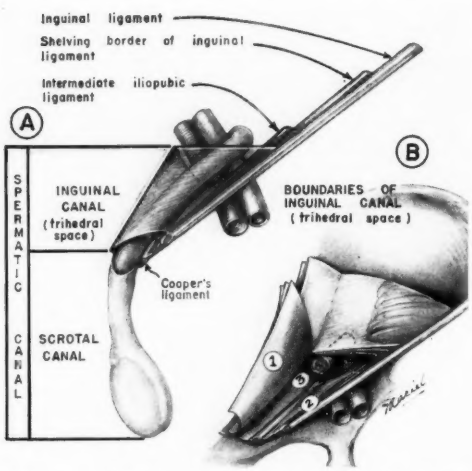

Fig. 1. A, The spermatic canal is illustrated which is divided into its two components: the inguinal canal and scrotal canal. The trihedral space of the inguinal canal is emphasized. The three longitudinal iliopubic ligaments of this region are shown. B, The boundaries of the inguinal canal and its contained trihedral space: *1*, Anterior plane, aponeurosis external oblique muscle, and internal oblique and transversus abdominis muscles. *2*, Inferior plane, inguinal ligament, its shelving border, intermediate iliopubic ligament, and interligamentous space. *3*, Posterior plane, fascia transversalis and Cooper's ligament. The anterior boundary is raised so as to better visualize the inferior and posterior boundaries respectively. The spermatic cord is sectioned at its entrance to the trihedral space.

the presence of the underlying external iliac vessels, the interligamentous space and the depth of Cooper's ligament at this transitional angle.

PARIETOPECTINEAL MANEUVER

The technique of the first maneuver has progressed through three successive stages of evolution. At its inception when introduced by Lotheisen and Narath, only the fascia transversalis was attached to Cooper's ligament. There was a lapse of some four decades before the second modification by McVay who sutured jointly the conjoined tendon and the fascia transversalis to Cooper's ligament. This ingenious yet logical technical modification created a bilaminar posterior wall or floor. As practiced in our clinic, all three abdominal strata are simultaneously anchored to Cooper's ligament retrofunicular (Fig. 2A). In addition special emphasis is placed on obtaining wide parietoligamentous surface contact by approximating the parietal wall to the entire internal vertical surface of Cooper's ligament. Moreover, we are convinced that the wider parietoligamentous contact obtained in the currently employed maneuver measurably augments the solidarity of the anchored wall (Fig. 2C).

The embarrassment, occasioned by the patient coughing at the critical moment of tying the completed first row of silk sutures with the result that many of them broke, has taught us to place greater confidence in fascia lata sutures, particularly in refractory and difficult hernias. A follow-up study of our series of 750 Cooper's ligament repairs confirmed this clinical impression by showing few recurrences in those cases in which fascial sutures were employed. Additive to the superior tensile strength of fascia, it more effectively bridges the vulnerable interligamentous space medially adjacent to the external iliac vein. Another of the manifold advantages of the fascial suture is that it provides greater elasticity of the repaired wall by dissipating a sudden thrust of intra-abdominal pressure, a characteristic which does not obtain in nonabsorbable heterogeneous sutures. In the event that there is deprivation of the wall, interweaving of the fascial suture, in effect, forms a taut dense stratum which remains viable for years.

In the first maneuver of Cooper's ligament repair, the following dynamic changes obtain: (a) there is a greater angle of inclination of a more deeply placed parietal wall which diverts the intra-abdominal pressure intrapelvically and away from the inguinal region; (b) the trihedral space, interligamentous space, and the spermatic cord are excluded; (c) the posterior wall is reinforced by converting it from unilaminar to a conjoined trilaminar floor.

INGUINOPECTINEAL MANEUVER

The interligamentous or inguinopectineal space lies subjacent to and forms, for the most part, the inferior boundary of the inguinal canal. Its closure has progressed segmentally through successive phases of repair

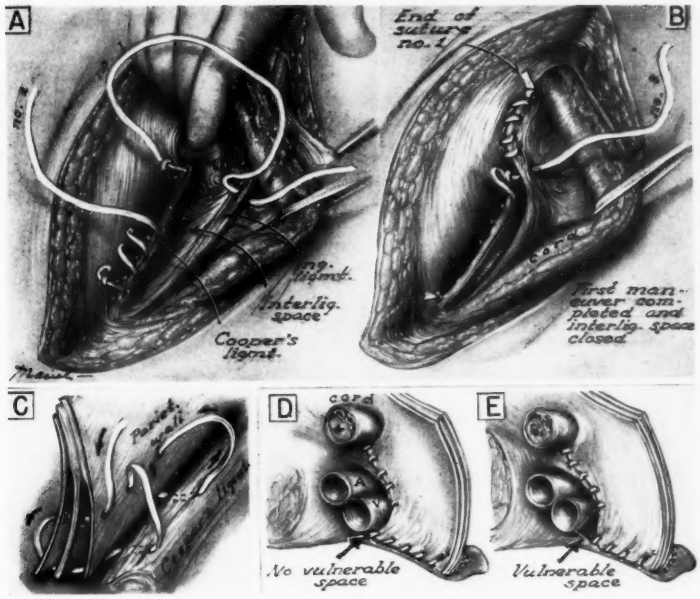

Fig. 2. First or parietopectineal maneuver. A, The first fascial suture is shown starting at the transitional angle, passing through the parietal strata and Cooper's ligament subjacent to the external iliac vein. The surgeon's index finger retracts and protects the vein during its placement. The suture has passed through the inguinal ligament preparatory to closing the transitional area. The second fascial suture has been started medially at the pubic tubercle and is shown progressing laterad. B, The first fascial suture is completed and shows completion of the first maneuver. The second suture is interlocked with the first preparatory to beginning the second maneuver. C, Insert is diagrammatic and illustrates the approximation of the parietal strata to the internal vertical surface of Cooper's ligament. D, Completed first maneuver as viewed from within. The arrow illustrates the closure of the vulnerable space. E, The arrow pointing to the persisting vulnerable space by failure to place the lateralmost suture in Cooper's ligament close enough to the external iliac vein.

beginning laterad and extending to the pubic spine. Because of the higher incidence of femoral hernia as compared to pectineal and translacunar hernias, one would quite naturally expect the earliest phase of Cooper's ligament repair to be focused on the closure, by various means, of the femoral ring adjunctive to the exsection of the femoral sac. Antedating this concept, it was generally accepted that removal of the femoral loculation of the sac subinguinally was sufficient for correction of this type of hernia. With cumulative clinical experience and follow-up studies, it was learned that an unrecognized concomitant inguinal sac and possibly a coexisting mural weakness of the posterior wall of the canal had frequently been overlooked which may be the source of a recurrence and often to the embarrassment of the surgeon. Because of the shortcomings of the femoral approach, it was obvious that attention must be directed to higher ligation of the sac, including any inguinal loculations, and to strengthening the floor of the canal additive to the all important maneuver of closure of the femoral ring.

Various ingenious methods have been devised for closing the femoral ring. The earliest to be described was by Annandale (1876) who obdurated the ring with the redundant portion of the ligated sac. Ruggi (1893) obliterated the ring by suturing the posterior edge of the inguinal ligament to Cooper's ligament. Where the ring is small

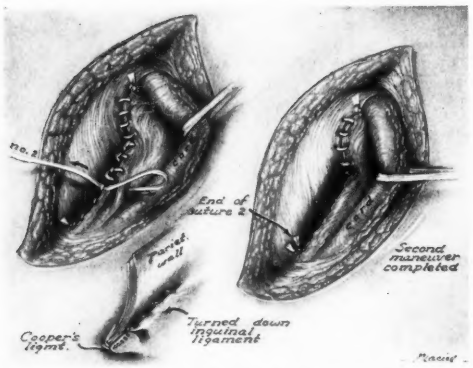

Fig. 3. Second or inguinopectineal maneuver. In the upper left drawing the edge of the inguinal ligament is in the process of being attached to Cooper's ligament. This suture passes through the loops of the previously placed fascial suture employed in the first maneuver. The upper right drawing shows the second maneuver completed. The insert is a cross-section of the two maneuvers illustrating the dual attachment to Cooper's ligament. Note the broad contact of the parietal wall to Cooper's ligament in contrast to the edge contact of the turned down inguinal ligament.

and with an elastic pliable inguinal ligament which can be approximated to Cooper's ligament without tension, the latter is a very satisfactory procedure. To obtain better exposure of Cooper's ligament, Ruggi ligated the inferior epigastric vessels. This maneuver alone, at such an early period of surgery, was an advance step which should have earned special recognition. In those instances in which there is attenuation and diffuse bulging of the medial lacunar ligament or where the femoral ring is inordinately large, Moschcowitz and Seelig and Tuholske closed the interligamentous space by suturing the recurved edge of the inguinal ligament which probably included the intermediate iliopubic ligament to Cooper's ligament. Since the space is triangular with its apex near the pubic spine, the ligamentous approximation is easier and there is less tension on the sutures if they are laid medially first and then progress laterad to the external iliac vein. When the inguinal ligament is taut and the interligamentous space wide, Carscadden, Payne, and Cowell have employed pedicled sutures of the external oblique aponeurosis to bridge this space. Gallie and LeMesurier and Burton (2) have preferred a free fascia lata suture to span the interligamentous space. A still more effective and simpler means of bridging the entire space is by turning down the cut edge of the inguinal ligament and suturing it to the anterior surface of Cooper's ligament. In the latter method, Cooper's ligament serves as dual anchorage for both the inverted inguinal ligament and the parietal wall. The latter, however, is attached to the internal flat surface of the ligament which is perhaps 1.5 centimeters deeper than the former (Fig. 2C).

Occasionally, it may be necessary to replace the inguinal ligament, especially in those patients who have irreparable or fragmented ligaments. Such a deficiency is usually acquired and in most instances arises from suture tension necrosis of previous operations. Turner, Wadhams and Carabba, and Wilmoth recognized the reparative significance of this type of almost total ligamentous insufficiency and proposed quite similar techniques for its replacement. A rectangular flap of fascia is raised from the anterior surface of the tensor fascia femoris muscle, slightly longer and wider than the normal inguinal ligament; it is then passed through the inferior boundary of the inguinal ligament juxtalateral to the external iliac vessels. The posterior edge of the flap is sutured to Cooper's ligament fixing it in its inguinopectinealized position. This maneuver provides not only a new inguinal ligament but simultaneously bridges the interligamentous space. An objectionable feature of this procedure is the thinness of the fascial flap consisting of only the anterior fascial envelope of the tensor fascia femoris muscle, and consequently, it does not wholly supplant an inguinal ligament of normal density.

Still another rather novel idea has been proposed for overcoming deprivation of the inguinal ligament by the employment of a massive pedicled graft of the iliotibial tract. DeGaray, Wangensteen, and Burton and Ramos (4) have reported their experiences with this technique. The graft may be brought anterior to the remnant of the in-

guinal ligament or it may enter the inguinal canal through the enlarged femoral ring. The graft is then fanned out and sutured to the medial fascial boundary, paralleling the semilunar line, to form the posterior wall of the inguinal canal. To attain a more resistant floor, the graft may be folded on itself thus doubling its thickness where it is strategically most important. Coincidentally, this technical variant excludes the interligamentous space or any attenuated or fragmented inguinal ligament. Although this technique is anatomically sound, it has become obsolete for the reason it is a more formidable procedure and the results no better than the standard Cooper's ligament repair.

Technique. Of the numerous methods that have been described for the closure of the interligamentous space, the inversion of the inguinal ligament, if present, and stitching it to Cooper's ligament is by far the most satisfactory, simplest to perform, and the one employed almost exclusively in our clinic during the last few years. We are accustomed to referring to this maneuver as *pectinealizing the inguinal ligament.* It will be noted from the illustration (Fig. 3) that only the cut edge of the inguinal ligament is brought in contact with the anterior superior surface of Cooper's ligament in contrast to the wider surface contact that obtains in the first maneuver. Moreover, it is not as deeply placed as the latter. If an autogenous fascial suture is employed in the first maneuver the suture anchoring the edge of the inverted inguinal ligament passes through the loop of the underlying suture thus obviating further needling of Cooper's ligament. Curiously enough, means devised for the obliteration of the resulting sulcus between the pectinealized walls gave impetus to the last or integrating step of the composite operation.

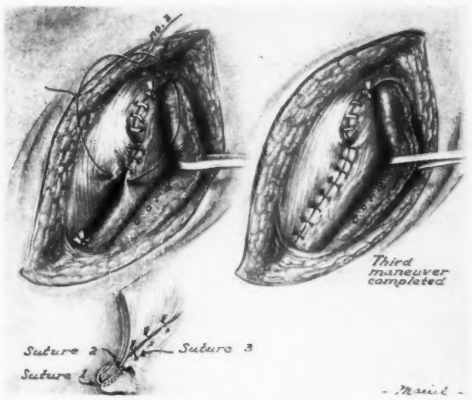

Fig. 4. Third or combined maneuver. The parietal wall is sutured to the adjacent anterior surface of the inguinal ligament creating a synthesis of the two walls but retaining their dual attachment to Cooper's ligament. Coincidentally the sulcus overlying Cooper's ligament is obliterated.

COMBINED MANEUVER

In most instances, it perhaps requires a decade from the time a new technique is conceived until it attains significant recognition. During the trial period, it must survive the all important test, that of practical application by many surgeons with an adequate and carefully checked follow-up period verifying its superiority before it becomes a standardized procedure. Apropos, the combined maneuver was reported in 1949 (3) although it had been employed in selected cases in our clinic some 5 years prior to that publication. During this interim, there has not been any substantial change in the original technique. However, the criteria for its employment have broadened, and, simultaneously, we have gained a better understanding of the dynamics of its anatomic and surgical background. We no longer think of this maneuver as simply the uniting of the superior and inferior walls with their dual pectinealization which obtain in the first and second maneuvers, but are recognizing more clearly that it is actually an integration of two standard procedures, inguinal ligament repair and Cooper's ligament repair. The significance of this achievement is that it compounds the crucial reparative elements of both operations. It is this additional knowledge which has been gained that we wish to emphasize.

There is unanimity of agreement based upon cumulative statistical and clinical studies that pectinealizing the parietal strata, if done so as to attain firm synthesis to Cooper's ligament, will give a uniformly strong wall in a high percentage of cases. With the pro-

posed combined technical innovation, it becomes necessary to re-evaluate the second or inguinopectineal phase. If only two maneuvers are employed in Cooper's ligament repair, it is, of course, difficult to justify the inguinopectineal maneuver for the obvious reason that it is not integrated with the first maneuver and remains strategically an independent maneuver. Since the second maneuver resulted in no strategic gain, we were left in a dilemma as to the advisability of abandoning it. However, the introduction of a third maneuver changed this perspective decidedly.

At this stage of the composite operation, both the parietal wall and the inguinal ligament have been pectinealized. It will be noted that the murofascial attachment to Cooper's ligament is made first which is the reverse of its technical evolution. The reasons for this are: (1) better exposure of Cooper's ligament at this stage of the operation; and (2) the loops of the underlying fascial suture are routinely used for the inguinopectineal anchorage, thus avoiding excessive needling and possible fragmentation of the ligament. If silk is employed for the first row of sutures, the ends are left long after tying in order to facilitate rethreading of the suture which is then passed through the edge of the inverted inguinal ligament. Because of less suture tension, tying of the ligatures is started medially near the pubic spine where the interligamentous gap is narrowest. On again referring to Figure 4, it will be noted that the parietal wall is attached as low as possible to the internal flat surface of Cooper's ligament so that a rather wide, tangential parietoligamentous contact obtains; whereas, when the inguinal ligament is turned down, there is for the most part, only contact with the edge of the latter as shown in Figure 3. Therefore, the much wider zone of parietopectineal synthesis is advantageous in augmenting and maximizing its solidarity. As a result of the two independent technical maneuvers, there is co-anchorage to Cooper's ligament. Simultaneously, there is created a pectineal or intermural angle between the converging walls with the superior pubic ramus forming the apex of the pectineal angle. It occurred to us that a stronger repair would accrue if the parietal and ligamentous walls were united suprajacent to Cooper's ligament.

Technique. The third or integrating maneuver of Cooper's ligament repair consists in suturing the crest of the convex surface of the inverted inguinal ligament to the adjacent previously pectinealized anterior parietal wall. By referring to Figure 4, it is readily seen that this simple additive maneuver creates a vertical tangential synthesis or raphe acting as a central tendon which is narrowest at the pubic spine gradually increasing in height until reaching the transitional juncture. There occurs simultaneously triple anchorage of the parietal wall with a direct or primary attachment to Cooper's ligament, an indirect connection through the intermediary inguinal ligament which has been surgically attached to Cooper's ligament, and a remote but measurable third retentive force from the anatomic origin and insertion of the inguinal ligament. The integrating maneuver of the composite operation obliterates the formerly excluded trihedral space. Coincidentally, it diminishes the former vallecula overlying the superior pubic ramus which invariably obtains on completion of the first two steps of the operation. Another important structural transformation occurs in that the transvascular portion of the transitional space is obliterated. The interligamentous space excluded by the inguinopectineal maneuver remains unchanged. The rostral end of the combined wall abuts the external iliac vein, thereby furnishing additional implementation of this vulnerable paravascular area. The spermatic cord which is translaminal subjacent to the abdominal ring is routinely deposited on the united walls so that the contour of the abdominal wall presents only slight depression in the inguina. Moreover, the conversion of the independent maneuvers into the combined repair by the addition of the third maneuver prolongs the operation only a few minutes. In our experience with the new technique which covers 8 years, there has been no increase in the incidence of femoral thrombosis. However, one should exercise

gentleness in retracting the external iliac vein.

After having become familiar with the triple maneuver technique, it is equally important to know when it should be employed. The criteria which we have used are: (1) attenuation of the inguinal ligament; (2) interligamentous hernias, including femoral, pectineal, translacunar, and transitional; (3) diffuse mesenchymal weakness; and (4) refractory hernias which include large sliding hernias and most recurrent hernias. It is not intended to imply that one should not consider other bizarre or equivocal mural weaknesses. Of course, the clinical evaluation of the latter will vary with the experience of the surgeon.

SUMMARY

The evolution of the combined maneuver of Cooper's ligament operative procedure has been described. The combined technique augments the security of the wall by creating a triple anchorage of the parietal wall; in contrast, the standard Cooper's ligament technique which is in general use consists of only a single or primary insertion of the wall to Cooper's ligament.

The boundaries of the trihedral space and their relation to the inguinal canal have been discussed.

The first step of the operation has been known and practiced for several decades but has not been popular. Similarly, the second step has been employed infrequently. The third or integrating step has been previously described and illustrated by the author. However, its significance was not sufficiently stressed. Subsequent clinical experience with this maneuver has served to steadily increase our confidence in its efficacy. It is rapidly becoming almost routine in Cooper's ligament hernia repair in our clinic.

Perhaps on critical evaluation of this advance step of the operation, the question may arise as to the necessity for either the second or third maneuver, assuming the integrity of the initial trilaminar parietal attachment to Cooper's ligament. The answer is forthcoming and quite convincing after combining the first two maneuvers which maximizes the reparative effect of all available structures of the inguinopectineal region.

Anyone who has followed the literature on the evolution of the surgical treatment of hernia can sense the changing attitude from the inguinal ligament repair to the deeper Cooper's ligament repair. The latter is not static but is undergoing successive modifications. The propensity to pectinealize simultaneously the inguinal ligament and the parietal wall is becoming increasingly more evident. As surgeons, we are constantly striving for improvements in technique. It is believed that there are valid reasons for considering the third maneuver as a progressive step in the surgical treatment of certain types of refractory hernias which are notoriously difficult to repair.

CONCLUSIONS

1. The standard maneuvers of Cooper's ligament repair have been discussed including rationale leading to the necessity for their development.

2. The relationship of the first maneuver to the trihedral space and the two standard maneuvers to the third maneuver of Cooper's ligament repair has been illustrated.

3. The triple maneuver is characterized by dual anchorage to Cooper's ligament with coincidental intermural synthesis. Strategically, it is an inordinately strong repair.

4. The proposed technical modification is simple of execution, does not prolong the operation appreciably, and can be done on all patients who have an intact inguinal ligament.

5. The criteria for the triple maneuver Cooper's ligament hernia repair have been enumerated.

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EOSINOPHIL AND URINARY CORTICOID CHANGES AS RELATED TO PITUITARY-ADRENAL-LIKE FUNCTION IN PREGNANCY

IRWIN SCHOEN, M.D., Long Beach, California, and
DAVID SCHNALL, M.D., Philadelphia, Pennsylvania

THE changes in the absolute eosinophil count have been shown to be useful as a specific index of adrenal function by Thorn and others. The values for urinary neutral reducing lipids, urinary formaldehydogenic lipids, and urinary glycogenic lipids have also been shown to be related to adrenal function. The following correlations have been proved by, or suggested from, studies concerning the level of adrenocortical or adrenocorticotrophic activity. With increased or increasing adrenocortical function, the eosinophils decrease and the urinary corticoids increase. With decreased or decreasing adrenocortical function, the eosinophils increase and the urinary corticoids decrease. The purpose of this paper is to demonstrate the nature of increased pituitary-adrenal function during pregnancy by using the two indices, eosinophil counts and urinary corticoids.

METHOD AND MATERIALS

Direct eosinophil counts were done by utilizing the eosin-acetone and phloxine-propylene glycol diluents of Hills and his associates and Henneman and his associates respectively. They were performed on oxalated venous blood drawn in the late afternoon or evening. For each count, the number of cells counted was multiplied by the factor 0.78 to give the final count in terms of the number of eosinophils per cubic millimeter of blood. The data consist of serial counts for each patient and were obtained from a heterogeneous group of 20 hospitalized pregnant women. The group consisted predominantly of mild hypertensives and mild pre-eclamptics without excessive edema; 1 case each of proteinuria, anemia of pregnancy, and inactive rheumatic heart disease; and 2 cases each of fetal deaths and normal pregnant women. Postpartum changes consisted of the comparison of the third to fifth day postpartum values with prepartum eosinophil counts taken within 3 to 20 days (most often less than 10 days) before delivery. They were evaluated in 19 of the patients. In calculating the postpartum per cent changes, the prepartum value was the average value of counts obtained within a period of less than 7 days in those cases in which more than one count was done; otherwise single prepartum counts were used.

The quantity of urinary formaldehydogenic corticoid excreted in 24 hours was determined for 7 of the prepartum patients. These formaldehydogenic assay data were compared to the eosinophil data of the same patient to demonstrate an eosinophil-corticoid correlation.

To substantiate our findings on individual patients, data for average eosinophil and average urinary corticoid values were obtained from the literature.

DATA AND RESULTS

Prepartum changes in the level of circulating eosinophils were evaluated in 2 patients followed during a considerable portion of their pregnancy. In Figure 1, C.G. showed an appreciable fall in eosinophils from the seventeenth week of pregnancy to 1 week before a premature delivery. B.F. showed a well defined progressive fall from the twenty-fourth week of pregnancy to term. Both patients evidently showed a fall in eosinophils with the increasing duration of pregnancy.

Postpartum changes in the eosinophil count were evaluated in 19 patients. In Figure 2a, 7 patients with uncomplicated delivery and lying-in period had a characteristic striking postpartum rise in the eosinophil count in every instance. By contrast, 11 patients with

TABLE I.—COMPILATION OF CHANGES IN THE LEVEL OF CIRCULATING EOSINOPHILS DURING THE PREPARTUM AND POSTPARTUM PERIODS

Eosinophil count changes													
Prepartum period				Postpartum period (days)									
A		B		C		D			E			F	
Weeks of Pregnancy	Per cent change	Day to day var. in a given week		Uncomplicated Per cent change	**	Infections Per cent change	**	Temp. *	Stillbirth and fetal deaths Per cent change	**	Time interval	Transfusion reaction	Per cent change **
B.F. 24	−66	I.G.	+ 4.3	E.B.	+175(3)	M.M.	+ 93(3)	102°	F.C.	+97(3)	>7 d	R.P.	− 24(3)
34	−56	C.O.	+ 5.8	M.W.	+500(4)	C.J.	+ 52(3)	100.4°		+ 7(5)			− 98(8)
38	−77	E.H.	−14.6	P.M.	+198(4)		+153(5)	Norm.	L.W.	+27(3)	2 hr.	R.B.	−100(2)
C.G. 17	−21	F.R.	− 1.5	H. Cox	+102(3)	C.M.	+119(3)	103°		+90(5)	72 hr. labor		
34	−74		+ 7.2		+150(5)		− 44(6)	102°		+50(7)			
		P.M.	+20	L.B.	+103(3)		+209(12)	Norm.	F.R.	− 4(3)	>5 d		
		C.J.	+13	C.G.	+163(3)	F.H.	− 2(3)	100.4°					
		F.C.	+ 6.2		+159(5)		+52(5)	100°					
		B.F.	+32	F.A.	+116(5)	A.S.	+61(2)	100.4°		Major surgery(*)			
			− 4				+140(6)	Norm.	B.F.	+65(3)			
		M.W.	+27				+125(9)	Norm.		+44(5)			
		C.R.	−31										
		F.A.	−28										
		H. Cox	+ 1.9										
		E.B.	+17										
Range: −21 to −77% Mean: (−59%)		−34 to +32% (−4.1%)		+102 to +500% (+185%)		−2 to +119% (+60%)			−4 to +97% (+47%)			−24 to −100% (−74%)	

*Surgical sterilization procedure was done on first day postpartum.
**Indicates the number of days postpartum in parentheses.

complicated delivery and, or, lying-in period and 1 unusual patient, H.C., showed a lessened or no postpartum rise, or even a fall in the eosinophil count, depending upon the character of the complication. In Figure 2b, 5 patients with the puerperium complicated by a postpartum infection or fever had only a moderate rise; when clinical recovery resulted, as indicated by the return to normal temperature, the previously noted marked rise in eosinophils (shown by the hatched segments of the curves in 3 cases) then took place. In Figure 2c, there are 2 cases in which fetal deaths occurred during the last trimester of pregnancy followed by delivery in approximately 1 to 2 weeks. F.R. showed a relatively high prepartum value and no significant postpartum change, and F.C. showed a second day moderate rise and a fifth day fall to prepartum values. Also in Figure 2c, 1 patient, L.W., with a 72 hour labor and subsequent stillbirth, had only a moderate eosinophil postpartum rise. In Figure 2d, B.F., with a 52 hour labor and on the first postpartum day a major surgical procedure for sterilization, had a slight postpartum rise in eosinophils. Also in Figure 2d, H.C. represents an interesting com-

TABLE II.—COMPARISON OF ABSOLUTE EOSINOPHIL COUNTS PER CUBIC MILLIMETER IN STERNAL MARROW AND PERIPHERAL BLOOD DURING PREGNANCY

Period of pregnancy	Marrow		Peripheral blood
	average	range	average
First trimester	371	48–1140	205
Second trimester	299	18–990	108
Third trimester	228	0–700	88

These data show a fall of eosinophil counts in marrow and peripheral blood with the progression of pregnancy.

plete absence of eosinophils in both the prepartum and postpartum periods. Finally, in Figure 2e, 2 patients with transfusion reactions postpartum had a marked fall in eosinophils; R.B. had a period of anuria with a zero count which rose abruptly with clinical recovery; R.P. required manual removal of the placenta with no postpartum rise, which was followed by a transfusion reaction with a marked fall in eosinophils.

Table I is a compilation of the changes noted in the pregnancy patients just described and shows values for the per cent changes of eosinophils during the prepartum and postpartum periods. In the prepartum period as shown in column A, there is a prepartum fall from about 17 weeks of pregnancy to term with a range of −21 to −77 per cent, and a mean of −59 per cent. Column B shows the day to day variation in eosinophils over an interval of less than 1 week (in the last trimester and before the onset of labor). The values were obtained by comparison of subsequent counts with the initial count and were between −34 to +32 per cent, with a mean of −4.1 per cent. During the postpartum period, on the third to fifth postpartum day, in column C for uncomplicated cases, there was a characteristic rise in eosinophils of greater than 100 per cent, that is from +102 to +500 per cent with a mean of +185 per cent. In complicated cases the third to fifth day postpartum rise was less than 100 per cent. The 1 exception was in a very toxic case of endometritis (column D); this patient showed a transient third day rise of +119 per cent. The patients in the infection group (column D) had changes in eosinophils from −2 to +119 per cent with a mean of +60 per cent. The group with fetal deaths, prolonged labor, or major surgery had changes of from −4 to +97 per cent with a mean of +47 per cent; and the 2 cases with transfusion reactions had even a fall in eosinophils with changes of from −24 to −100 per cent and a mean of −74 per cent.

To demonstrate an eosinophil-corticoid correlation, in 7 of the cases during the prepartum period formaldehydogenic urinary lipid values were determined. These values were each compared to an eosinophil count done for the same patient on the same day as, or within 3 days of, the date of urine collection. The curve drawn in Figure 3 shows a reciprocal relationship between urinary corticoid values and eosinophil counts for individuals with different levels of "adrenal" function.

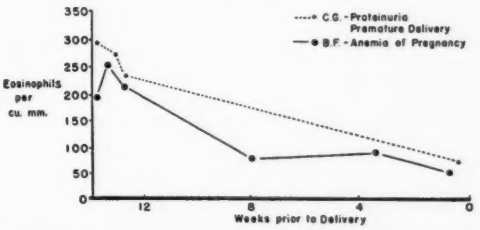

Fig. 1. In 2 cases, a fall in eosinophils during pregnancy is noted without change in the prepartum clinical course.

From the literature the following findings and data for average urinary corticoid and eosinophil values were gathered to confirm the changes in individual patients during the prepartum and postpartum period just described. For the eosinophil changes Pitts and Packham show a definite progressive fall in the marrow and peripheral blood during pregnancy. These data in Table II are based upon calculations from the total white cell and differential counts. Rath and associates interpreted their data from direct chamber counts for eosinophils in the peripheral blood, so that one may assume about a 20 per cent drop during early pregnancy and a 30 to 40 per cent drop in late pregnancy. The data recorded in Figure 4 and calculated from Sturgis and associates are based on total white cell and differential counts. They show a progressive fall in eosinophils during pregnancy with a postpartum rise and then a falling off to prepregnant levels. Davis and Hulit show a mean direct eosinophil count of 180 per cubic millimeter for adult normal nonpregnant females, whereas that for pregnant women is 90 per cubic millimeter throughout all periods of pregnancy; the fact that Davis' data do not reveal a fall during the progression of pregnancy will be discussed later. Davis also shows an average postpartum rise similar to our findings.

From various literature sources for average values data were accumulated to substantiate the quantitative reciprocal eosinophil-corti-

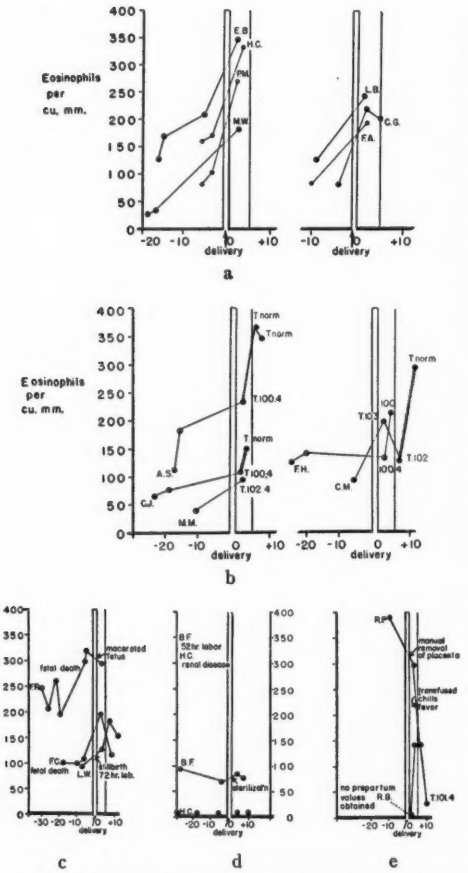

Fig. 2. Postpartum changes in levels of circulating eosinophils. a, In uncomplicated puerperium a marked rise 3 to 5 days postpartum is shown. b, In complicated puerperium, puerperal fever, is shown a lessened rise due to infection followed by marked rise when afebrile (indicated by the hatched segments of the curves). c, In complicated pregnancy, fetal death and prolonged labor with stillbirth, lessened to no postpartum rises are indicated. d, In complicated pregnancy, prolonged labor and major surgery, on the first postpartum day no significant rises are shown; an unusual case shows no eosinophils in the prepartum or postpartum periods. e, In complicated puerperium, transfusion reactions, a marked fall in the level of circulating eosinophils is noted.

coid correlation. These were noted in the changes during pregnancy, with the level of eosinophils decreasing as the level of urinary corticoids increased during the prepartum period, and the level of eosinophils increasing as the level of urinary corticoids decreased during the early postpartum period. In Table III, the mean values for normal nonpregnant women and pregnant women in the last trimester show an equivalent quantitative inverse ratio relationship between eosinophils and urinary corticoids. Even more suggestive and interesting is Figure 4 in which the variations of mean urinary glucocorticoids and the variation of average eosinophil values during pregnancy and the postpartum period show a striking correlation; the change in eosinophils is practically a mirror image of the curve showing corticoid changes. The curve for the average urinary glucocorticoid changes in the prepartum period is from Venning (18) and the postpartum portion is an extension from additional data in her article. In Figure 5 there are plotted pregnancy data for average urinary neutral reducing lipids from Parviainen and associates and for average direct eosinophil counts from Rath and associates obtained from smaller groups of cases than the data in Figure 4. Approximate smooth mean curves reveal a similar inverse relationship between urinary corticoids and eosinophils.

From various sources, in Table IV, the average intervals required for the levels of eosinophils and urinary corticoids to return to normal or recover after surgery, parturition, and cessation of ACTH therapy have been compared. Note then that eosinophil and corticoid recovery takes place in 2 to 4 days after ACTH therapy cessation or withdrawal in a comparable 3 to 5 days after parturition and in 4 to 11 days after major surgery. Together with the data presented on individual patients, these led to the identification of an ACTH-like withdrawal phenomenon associated with the delivery of the placenta to be discussed further.

DISCUSSION

Although our data were obtained on a heterogeneous group of hospitalized pregnant women, predominantly mildly toxemic and hypertensive patients, it is probable that our data are equivalently representative of normal pregnancy especially in view of the findings accumulated from the literature. When adrenal

function is measured by urinary corticoid excretion, Tobian showed that there is no difference between normal pregnant women and mild pre-eclamptics without excessive edema, or between the normal female and hypertensive female. Also Bernstine and DeAndino were unable to show any difference in eosinophil counts between a group of toxemic and normally pregnant women. These two observations further substantiate the view that our data are probably representative of normal pregnancy.

All the evidence presented demonstrates decreasing levels of eosinophils and increasing levels of urinary corticoids with the progression of pregnancy except for Davis' data on eosinophils. These data revealed a mean value of 180 eosinophils per cubic millimeter for normal nonpregnant females and a significantly lower average value of 90 per cubic millimeter for pregnant women throughout all periods of pregnancy. A fall in eosinophils had taken place but its progressive nature might have been masked. This may have been due to variables introduced because apparently the counts recorded were single counts on different women in various periods of pregnancy. Eosinophil counts vary more markedly from person to person than in a given individual, and also routine calculated periods of pregnancy may have an inherent error of plus or minus 1 month.

The data of Pitts and Packham showing a decrease in the number of eosinophils in the marrow can be explained by the fact that Muehrcke and associates and Godlowski have shown that 11–17 oxycorticoids may have a specific direct humoral effect on the eosinophils. One might then expect a similar change in the marrow as that in the peripheral blood.

The lessened rise or even fall of eosinophils in the complicated postpartum cases, as compared to the characteristic rise in uncomplicated cases, is probably based upon the stressor characteristics of the complications and their relative severity. Stressors have been previously noted to produce a fall in the level of circulating eosinophils. In those cases complicated by puerperal fever the delayed rise in eosinophils after the return to normal temperature indicated removal of the stressor and a favorable state of convalescence from the postpartum infection. The interesting finding, in the 1 case, of no circulating eosinophils in the prepartum and postpartum period recalls a quotation from Sturgis: "Although

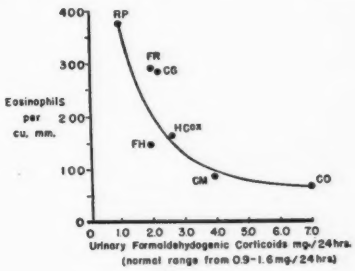

Fig. 3.

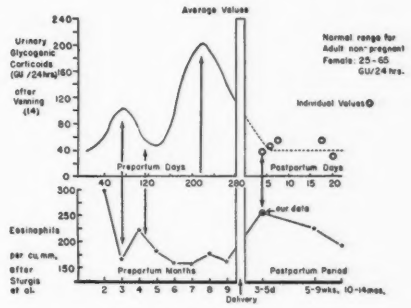

Fig. 4.

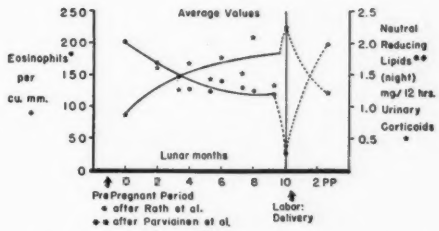

Fig. 5.

Fig. 3. Prepartum patients with a comparison between their eosinophil counts and the amount of urinary formaldehydogenic corticoid excreted.

Fig. 4. The urinary glucocorticoids and eosinophils show a striking inverse relationship in the prepartum and postpartum periods; the eosinophils decrease while the corticoids increase with advancing pregnancy and both return to prepregnant levels postpartum.

Fig. 5. Eosinophil-corticoid correlations in pregnancy indicate the eosinophil counts fall and neutral reducing lipids increase with the progression of pregnancy, with the eosinophils rising after delivery and the corticoids falling toward prepregnant levels.

TABLE III.—AN EOSINOPHIL-CORTICOID CORRELATION FOR AVERAGE VALUES

	Eosinophils* per cu.mm.	Urinary corticoids** (formaldehydogenic) mgm./24 hrs.
Normal women	180	0.47
Pregnant women (normal) (30–40 wks. pregnant)	90	0.95
Ratio of nonpregnant women to pregnant women	2:1	1:2

*After Davis and Hulit
**After Tobian
The data present a quantitative inverse eosinophil-corticoid relationship when comparing nonpregnant normal adult females with pregnant women in the last trimester of pregnancy.

complete absence of eosinophils from the circulating blood must be considered abnormal it is difficult to interpret the exact significance of this finding."

The data presented for changes in eosinophils and urinary corticoids provide reasonable proof that there is increased adrenocortical-like activity during pregnancy which increases with the duration of pregnancy. Since the level of circulating eosinophils has been shown to correlate so well with the values for urinary corticoids, for both biologic and chemical assays, and since it is known that the level of circulating eosinophils is specifically influenced by 11–17 oxyglucocorticoids, this increased adrenal-like function is most likely predominantly 11–17 oxyglucocorticoid in nature. The striking characteristic postpartum third to fifth day rise in eosinophil count (and especially its absence in the 2 cases presented of prepartum fetal deaths and uncomplicated postpartum period) together with the apparent abrupt postpartum fall in urinary glucocorticoids suggested the probability that this was an adrenocortical or adrenocorticotrophic hormonal withdrawal phenomenon. The time factors in Table IV are in accord with this hypothesis, as the postpartum eosinophils and urinary corticoids behave more like the changes following the cessation of ACTH therapy than like the reaction to stress, such as major surgery. The third to fifth day rise in eosinophils of greater than 100 per cent described in the uncomplicated postpartum period may be presumed to be related to the recovery from the acute stress of parturition comparable to the stress changes in some patients with acute coronary occlusion or with minor surgical procedures as noted in data from Gabrilove. That the change in eosinophils is not explained by the stress of normal parturition is suggested by the absence of this characteristic change in the cases of fetal deaths described. Corticoid recovery in patients with Cushing's syndrome undergoing major surgery is delayed 10 to 15 days. If pregnancy is a manifestation of chronic stress with a superimposed acute stress of delivery the eosinophil-corticoid recovery might have been expected to be delayed instead of as noted. Therefore, the eosinophil-corticoid recovery seems most likely to be a hormonal withdrawal phenomenon.

TABLE IV.—ACTH-LIKE WITHDRAWAL EOSINOPHIL RECOVERY DURING POSTPARTUM PERIOD

	Eosinophil recovery ↑	Urinary corticoid ↓ recovery
ACTH withdrawal	2–4 days (16) (to previous level→+ 80%)	2–4 days (17)
Postpartum period	3–5 days (12) (>100%) (our data)	3–5 days (14)
Major surgery Postoperative period	4–11 days (2) (to levels>preop. lev. usually<+80%)	10–15 days (18)

The comparison of time factors and changes taking place in eosinophils and urinary corticoids suggests the presence of a hormonal withdrawal phenomenon related to parturition.

The small amounts of urinary corticoid excreted by the newborn and the refractoriness to epinephrine pituitary stimulation in the premature newborn make the fetus an unlikely source of the adrenocorticotrophic or adrenocortical activity during pregnancy.

In attempting to explain the elaboration of urinary glucocorticoids by the newborn, Venning (19) could not demonstrate glucocorticoid activity in placental extracts. By chromatographic means, Seneca and associates were also unable to identify the presence of cortisone in extracts of human placentas. Therefore, the postpartum hormonal withdrawal phenomenon is probably ACTH-like and placental in origin. Since the gonadotrophic production in pregnancy has been identified as being produced by the cytotrophoblast it was considered that the cytotrophoblast is producing another protein-like hormone, that is, ACTH. Subsequently, the presence of ACTH-like activity in placental

extracts has been reported independently by Jailer and Knowlton, by Tarrantino, and even in greater quantities than and potencies equivalent to pituitary ACTH extracts by Opsahl and Long. In addition Krebs states that they have isolated and identified cytotrophoblastic ACTH. These extraction studies do not differentiate storage from secretory significance of the ACTH in the placenta. However, the ACTH withdrawal effect described by the eosinophil and urinary corticoid data suggests a functional role played by the placental ACTH and, therefore, implies secretory rather than storage significance to the ACTH found in the placental extracts. Previously, pregnancy steroid secretion has been demonstrated for the syncytiotrophoblast. The inability of others to detect cortisone-like material in the placenta suggests the possibility that syncytiotrophoblast may not be the source of, or the only source of, placental steroids and that the decidua might be the source of steroidal hormones, especially corticoids, in pregnancy. Supporting this view is the suggested comparison showing the histologic similarity between the specialized stroma of the ovary, or theca cells with known steroid function, and the specialized stroma of the endometrium, or decidual cells with suggested analogous steroid function. Although the increase in adrenocortical-like function can be explained by the fact that the placental ACTH may be stimulating the maternal adrenal, the possibility of decidual steroid production exists.

The findings presented from our data for individual values and from the literature for average values show a significant striking inverse relationship between eosinophil counts and urinary corticoid assay values. Figure 3, especially, is very suggestive of a quantitative reciprocal eosinophil-corticoid relationship such that the absolute level of circulating eosinophils may be a useful measure of the level of effective adrenocortical function.

From our data and review of the literature, further studies correlating serial eosinophil counts and urinary corticoid assays on individual women throughout uncomplicated and complicated pregnancy and the nature of increased pituitary-adrenal-like function during pregnancy are indicated.

SUMMARY AND CONCLUSIONS

The nature of pituitary-adrenal-like function during pregnancy has been described in terms of changes in eosinophil counts and urinary corticoid values in the prepartum and postpartum periods. In the prepartum period there is a decrease in eosinophils and an increase in the urinary corticoids which represent increasing adrenocortical-like function. This fact is presumably based upon ACTH secretory activity of the placental cytotrophoblast and possibly decidual glucocorticoid production mediated by the placental ACTH. There is a characteristic striking third to fifth day postpartum rise in eosinophils and fall in urinary corticoids which are presumably related to the delivery or removal of the placenta and its hormones. A quantitative reciprocal correlation between the level of circulating eosinophils and the level of urinary corticoids for varying levels of adrenocortical-like function in pregnancy has also been demonstrated.

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THE ACUTE RED BLOOD CELL DESTRUCTION FOLLOWING SEVERE THERMAL TRAUMA IN DOGS

Based on the Use of Radioactive Chromate Tagged Red Blood Cells

JOHN W. RAKER, M.D., and RICHARD L. ROVIT, M.D., Boston, Massachusetts

RECENTLY several investigators have recommended the liberal use of whole blood transfusions as the basis of early replacement therapy for the fluid and colloid losses following severe thermal burns. This recommendation is based upon two premises: (1) that the magnitude of the acute destruction of red cells by thermal injury is large, and (2) that replacement therapy employing plasma as the main source of colloid is deficient in that it fails to supply red cells to replace those acutely destroyed. Since the acceptance or rejection of early massive whole blood therapy in burns depends upon the validity of these two premises, it has seemed important to us to reinvestigate the actual magnitude of the acute red cell destruction caused by thermal injury.

Following severe thermal injury an increase in capillary permeability occurs in the traumatized areas, which results in a massive exudation of protein, electrolytes, and water into the tissue interstices. If allowed to progress without therapy, this loss of plasma constituents from the intravascular compartment produces the classic picture of hemoconcentration, a rapidly rising hematocrit, diminution in urine flow, shock, and ultimate death.

During World War II studies made in the United States by Moore and associates and in England by Colebrook and co-workers disclosed a loss of not more than 7 to 10 per cent of circulating red cells following severe thermal trauma. These studies were carried out with radioactive iron and by analysis of tests of red cell fragility. Subsequent determinations by other investigators using the radioactive phosphorus and the blue dye T-1824 method of measuring red cell volume have placed this acute destruction of red cells following severe burns at a much higher figure. Using the radioactive phosphorus method, Salzberg and Evans reported an estimated loss of 43 per cent of circulating red blood cells in a young woman following second and third degree flame burns involving 75 per cent of her body surface.

However, there are certain practical and theoretic objections to the use of both radioactive phosphorus and blue dye T-1824 for the measurement of the destruction of red cells following burns. Radioactive phosphorus may be used to tag red cells quite successfully. However, phosphate ion is a normal constituent of the red cell and is involved in the metabolism of the red cell, and the loss of radioactive phosphorus across the red cell membrane after injection into the test object reduces the effectiveness of this material as a tag for red cells and as a measure of red cell volume. The radioactive phosphate transferred from the cells by normal physiologic processes would be added to the radioactive phosphate released into the plasma by hemolysis of damaged tagged cells. Thus by using P^{32} tagged red cells, one might be led to infer that a somewhat greater loss of red cells occurred following severe burns than would be disclosed by tagging the red cells with radioactive iron.

There are two important practical objections to the T-1824 method for calculating red cell volume in patients or animals that have suffered severe thermal injury: (1) the hemolysis caused by severe burns interferes appreciably with precise colorimetric determinations of T-1824 in the plasma, and (2) repeated determinations of plasma volume

From the Department of Surgery of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts.

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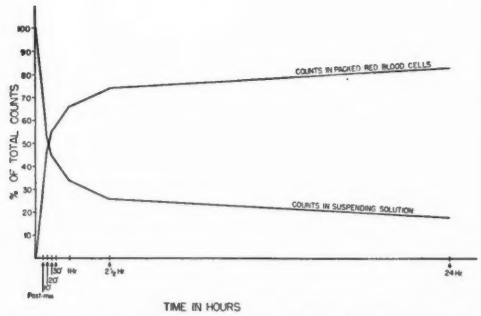

Fig. 1. Rate of uptake of radioactive chromium by red cells.

are limited by the intense blue color of the plasma following 2 or 3 injections of the dye.

In addition to these practical objections there is a theoretic objection to the use of T-1824 for the determination of red cell volume in burns. The determination of plasma volume by means of T-1824 depends on the formation of a stable linkage between the serum proteins, mainly albumin, and the dye. Observations made in this laboratory using albumin artificially tagged with I^{131} have shown that the increased capillary permeability of the burned areas permits a significant quantity of plasma protein to leak into the interstitial spaces. This observation makes us question the accuracy of any method using intravascular proteins as the basis of determining plasma volume following severe burns.

The use of radioactive iron for measuring the red cell destruction following severe burns has none of the theoretic disadvantages of the T-1824 and radioactive phosphorus methods. However, this method has two practical disadvantages: (1) suitable donors must be given radioactive iron for a period long enough to permit incorporation of the radioactive iron into the donor's own red cells, and (2) methods for recovering and determining the radioactive iron are time-consuming, and results of determinations are not quickly obtained.

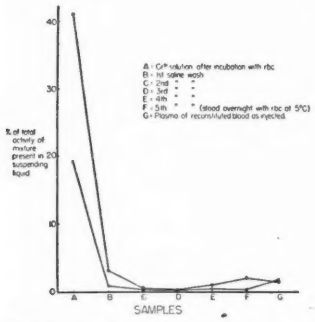

Fig. 2. Efficiency of washing in removal of Na_2CrO_4 excess.

When a method for determining red cell volume by means of cells tagged with radioactive chromium was developed by Sterling and Gray, it appeared that this method might combine the accuracy of the radioactive iron technique with the practical ease of the P^{32} technique in determining red cell volume.

We have attempted to assess the use of radioactive chromate as a method for tagging red cells and for the determination of red cell volume. We have used this method to measure the precise amount of red cell destruction that follows severe thermal trauma in a group of dogs burned by a standard technique.

METHODS AND PROCEDURES

Preparation of chromate tagged red blood cells. Thirty-five to 50 cubic centimeters of whole blood were removed from the cephalic veins of healthy adult dogs into a 50 cubic centimeter centrifuge tube containing 0.5 cubic centimeter of heparin. This blood was centrifuged immediately for 30 minutes at 2800 revolutions per minute. After centrifugation, the supernatant plasma was removed and stored in the icebox. Twenty to 30 cubic centimeters of sodium chromate in saline, containing 110 to 160 microcuries of Cr^{51} were then added to the heparinized red cells. These red blood cells, now resuspended in the sodium chromate–sodium chloride mixture, were incubated for 1 to 2 hours with constant mechanical shaking. At this time the red cells had acquired sufficient activity for subsequent use as tracers.

After centrifugation, the supernatant chromate-saline solution was removed, and the tagged red blood cells were washed 3 times with cold fresh physiologic saline solution to remove any excess radioactivity not firmly

bound to the red cells. The red cells, now firmly tagged with Cr^{51}, were resuspended in their original plasma and thoroughly mixed. A 7 cubic centimeter aliquot of this chromated blood was removed for determination of hematocrit and subsequent counting procedures. The plasma of this specimen contained 0.5 to 1.5 per cent of the counts present in red blood cells (Fig. 2). After the aliquot had been removed for counting, the remainder of this reconstituted blood measured 35 to 40 cubic centimeters. This was divided into two portions for subsequent reinjection into the animals.

The experimental procedures. Healthy dogs were used throughout these experiments. However, some of the animals, as judged by the color of their conjunctivae, their initial hematocrit, and the preburn determination of red cell volume may be assumed to have been moderately anemic prior to experimental thermal injury.

The animals were anesthetized with intravenously administered nembutal solution. The hair covering the anterior neck and lower two thirds of the body was removed with electric clippers. One internal jugular vein was exposed and a polyethylene catheter passed through it toward the heart until the end of the catheter lay in the superior vena cava. This catheter was accurately filled with dilute heparin solution to prevent coagulation, and the other end of the catheter was stoppered with a plastic cap fitted into a No. 18 needle. This catheter was used for the removal of all blood samples from the animal. The contralateral internal jugular vein was isolated and used for injections.

Ten to 15 cubic centimeters of the reconstituted blood were accurately measured and injected into the isolated jugular vein. Blood samples were obtained from the polyethylene catheter 20 and 30 minutes after injection and a drop of heparin was added to prevent clotting. The first cubic centimeter of all blood samples taken from the polyethylene catheter was discarded lest there be any heparin from the catheter contaminating the samples.

Eight dogs were immersed in water, at 85 degrees C., for 30 seconds so that about 50

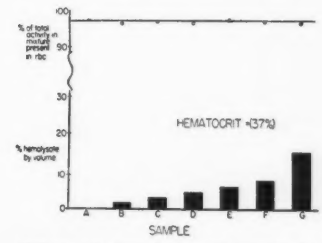

Fig. 3. Effect of hemolysate on counts in red blood cells.

per cent of their body surface was scalded. Three additional dogs suffered burns of the same area and temperature but were kept in the water for 3 minutes.

One hour after the animal was burned, the second portion of the reconstituted blood with Cr^{51} tagged red cells was injected into the internal jugular vein. In several experiments a third injection of tagged red cells was carried out 4 hours after the burn. Samples were obtained from the polyethylene catheter 20 and 30 minutes later. Subsequent samples were taken at hourly intervals for the next 4 to 5 hours. After all samples had been collected the animals were sacrificed.

Preparation of the samples. The aliquot of reconstructed blood containing tagged red cells ready for injection into the animal and all subsequent samples removed from the polyethylene catheter were handled in the same fashion. All samples were thoroughly rotated for 3 minutes to insure complete mix-

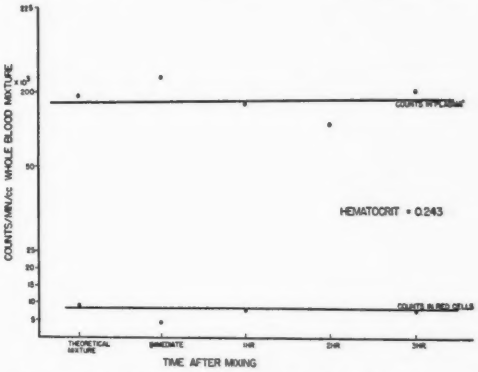

Fig. 4. Incubation of radioactive chromium tagged hemolysate with untagged red cells.

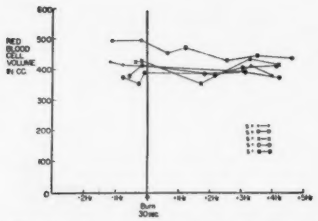

Fig. 5. Blood volume changes after 30 second burn.

ing of the whole blood. Two cubic centimeters of whole blood were then pipetted into fine bore hematocrit tubes and centrifuged at 2,800 revolutions per minute for 1 hour. The hematocrit was determined.

Two-tenths cubic centimeter of whole blood was pipetted into each of 3 aluminum planchettes containing 1 drop of tween-80 detergent solution. The whole blood sample was diluted to 1.0 cubic centimeter volume by the addition of 0.8 cubic centimeter of normal saline solution. The samples were thoroughly mixed and allowed to dry overnight.

After the removal of the aliquots for plating and determination of hematocrit, the remaining whole blood was centrifuged for 30 minutes at 2,800 revolutions per minute. The supernatant plasma was removed with a fine capillary pipette; 0.2 cubic centimeter of this plasma was then pipetted into each of 3 aluminum planchettes containing 1 drop of tween-80. The plasma samples were diluted to 1.0 cubic centimeter by the addition of 0.8 cubic centimeter of normal saline solution, thoroughly mixed, and allowed to dry overnight.

Counting of the samples. After all samples had dried, they were counted by means of a Geiger-Müller counting tube sensitive to soft gamma rays. Some of the more recent counting has been done by using a scintillation counter of the "well" type. All samples were counted for a period of time long enough to insure a counting error of less than 2 per cent. Corrections for background counts and for radioactive decay were made.

Cr^{51} is a soft gamma ray emitter, and experiment showed that there was significant self-absorption in the samples as the volume of packed red cells was increased. The amount of radiation lost by self-absorption was found to be proportional to the hematocrit, and it was possible to calculate correction factors based on this observation.

Calculations. After correction for decay of radioactivity and background, the average counts of the 3 planchettes were computed. The average count for the 0.2 cubic centimeter sample of whole blood was multiplied by a factor of 5 in order to obtain counts that would be present in 1.0 cubic centimeter of whole blood. All plasma samples were similarly handled.

On the basis of the hematocrit obtained on each sample of whole blood, that amount of plasma present in 1.0 cubic centimeter of whole blood was computed. The counts that would be present in such an amount of plasma were calculated from the counts in 1.0 cubic centimeter of plasma determined at the same time.

These plasma counts were subtracted from the total counts in 1.0 cubic centimeter of whole blood. The counts observed in the plasma samples were of the order of background unless hemolysis of tagged cells had

TABLE I

A—30 Second Burn

Dog No.	RBC volume before burn		RBC volume after burn		Per cent destruction	
	Highest c.c.	Average c.c.	Lowest c.c.	Average c.c.	Maximum	Based on average
V19	404	404	394	400	2.5	1.0
V20	222	215	198	203	10.8	5.6
V21	617	604	603	603	2.3	2.3
S1	424	417	382	395	9.9	5.3
S3	496	496	430	451	13.3	9.1
S8	429	427	367	406	14.5	4.9
S9	413	397	386	402	6.5	0.
S10	391	373	365	392	6.6	0.
				Average	8.3	3.5

B—3 Minute Burn

S6	184	184	115	125	37.5	32.1
S7	567	548	333	363	41.3	33.8
S11	427	411	250	263	41.5	36.0
				Average	40.1	34.0

taken place. When such hemolysis did occur as a result of the burn, the amount of radioactivity in the plasma was small in relation to the radioactivity present in the red blood cells, and counts in the plasma samples were proportional to the plasma hemoglobin concentration.

When the counts found in plasma were subtracted from those found in the corresponding whole blood sample, the remainder could be considered counts from Cr^{51} present in the red cells of 1.0 cubic centimeter of that whole blood sample. The correction for counts lost due to the self-absorption of the soft gamma ray by increasing thickness of the red cell layer was then made.

Since the samples did not all have the same hematocrit, all red cell counts were expressed as counts in 1.0 cubic centimeter of packed red blood cells.

The calculation of red blood cell volume:

$$\text{RBC volume} = \frac{\text{Total counts injected}}{\text{Counts per 1.0 c.c. of red cells present in sample}}$$

$$\text{Total counts injected} = \text{Counts per 1.0 c.c. of red cells in standard} \times \text{volume of red cells injected}$$

$$\text{Volume of red cells injected} = \text{Volume of standard reconstituted blood injected} \times \frac{\text{Hct.}}{100}$$

In all calculations there must be a small constant error because a fraction of the plasma is trapped with the red cells when the hematocrit tube is centrifuged. No correction is necessary for this error.

In calculating the red cell volume following a second injection of tagged red cells, the numerator in the equation given represents the additional increment of tagged cells. The denominator is the counts per 1.0 cubic centimeter of red cells in the sample taken after the second injection minus the counts per 1.0 cubic centimeter of red cells in the sample taken just before the second injection of tagged red blood cells.

RESULTS

Evaluation of the method. We have confirmed the fact that Cr^{51} in the form of the chromate ion is rapidly taken up by erythrocytes of dog or man (Fig. 1). These tagged cells retain the radioactive chromium so well that virtually no loss of radioactivity is noted during the several hours required to carry out an experiment in this series. When the cells are washed with saline, radioactivity is so completely removed from the suspending medium that 98 to 99 per cent of the total activity injected into the test animal is in the cells (Fig. 2).

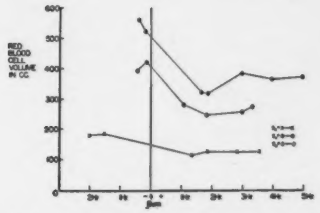

Fig. 6. Blood volume changes after 3 minute burn.

In repeated attempts at determination of blood volume in the same animal and in attempts at the determination of the volume of transfused cells by estimating blood volume before and after transfusion, this method has proved to be accurate within a range of error of 5 per cent of the total red cell volume. This is similar to the accuracy reported by Sterling and Gray.

Since the purpose of this study was to quantitate the loss of red cells by hemolysis after thermal injury, it was important to show that the presence of hemolyzed cells would not interfere with the determination of blood

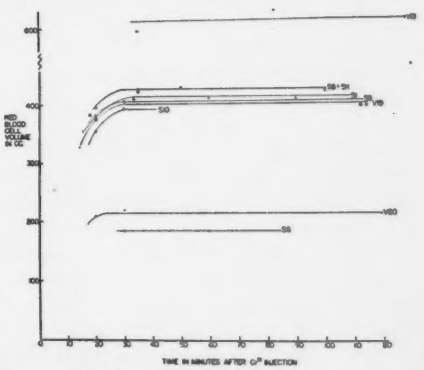

Fig. 7. Mixing time preburn.

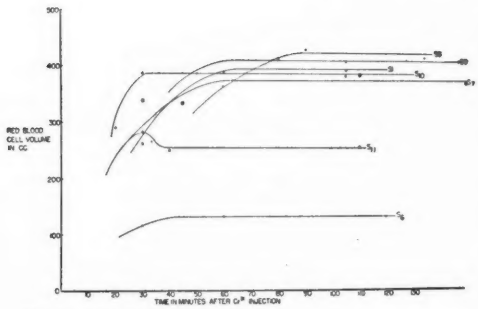

Fig. 8. Mixing time postburn.

volume by injection of Cr^{51} tagged intact red cells. Figure 3 shows the constancy of counts due to radioactivity in tagged red cells in spite of the addition of considerable volumes of untagged hemolyzed cells. The presence of hemolyzed cells does not interfere with the measurement of the activity in the intact cells. Tagged red cells do not lose Cr^{51} to the plasma even though large amounts of hemolyzed cells are added to the plasma.

It was also important to demonstrate that any hemolysis of tagged cells injected before the thermal injury would not interfere with determinations of blood volume after injury. Figure 4 shows that untagged red cells do not take up Cr^{51} which is in the hemoglobin circulating in the plasma as the result of hemolysis of tagged cells. If 5 per cent of the plasma is assumed to be trapped with the red cells when the mixture is centrifuged, the observed counts in the red cells correspond closely to the calculated counts which would be present in the trapped plasma. Figure 4 should be contrasted with Figure 1, which shows the avidity with which red cells take up chromate ion which is not fixed to hemoglobin.

Determinations of red cell volume done by injecting Cr^{51} tagged red cells 4 or 5 hours after thermal injury did not differ significantly from determinations done 1 hour after injury. The 1 hour interval was chosen for the majority of the experiments because it was more convenient.

Quantitation of red cell destruction. Eight dogs were subjected to 50 per cent body surface burns caused by immersion in water at 85 degrees C. for 30 seconds. A burn of this severity is often lethal for an untreated dog in 6 to 8 hours, and such burns are thought to be comparable to third degree burns commonly observed in humans who have suffered chance thermal injury. These 8 dogs have shown an average maximum red cell destruction of 8 per cent of the original red cell volume (Table IA and Fig. 5).

Three dogs were subjected to 50 per cent body surface burns caused by immersion in water at 85 degrees C. for 3 minutes. These dogs showed almost complete immobilization of the joints of the burned extremities with striking local edema and deep coagulation of muscle protein. There may be damage to tendons and ligaments as well. This damage is far in excess of that commonly seen in chance thermal burns of great severity. These dogs have shown an average maximum erythrocyte destruction of 40 per cent of the original red cell volume (Table IB and Fig. 6).

An attempt has been made to calculate the amount of hemolysis of red cells in these same dogs by utilizing the increase of counts in the plasma caused by the release of tagged hemoglobin into the plasma as the red cells are destroyed. This method of calculation is less accurate than the direct method of measuring hemolysis by difference in blood volumes, but it does give rough confirmation of the results of the latter method.

Simultaneous blood samples taken from veins draining burned and unburned areas have shown nearly identical hematocrits and radioactivity: the blood volumes calculated from these samples are nearly identical. This fact and the constancy of determinations of red cell volume for 4 or 5 hours after the burn argue against the possibility that any large "pool" of tagged or untagged undestroyed red cells exists in or near the burned area. We have not observed any decrease in radioactivity after thermal injury comparable to that observed by DeLorme and associates using P^{32} tagged red cells in animals in hemorrhagic shock. In our observations there is no evidence for the existence of a large reservoir of untagged cells available for release into the blood stream such as that postulated by those authors.

However, there is good evidence that the even distribution of blood throughout the body is slower after the development of burn shock than in the normal animal. In Figure 7 it is clear that 30 minutes after the injection of Cr^{51} labelled red cells in the normal animal the level of radioactivity in the peripheral venous blood has reached equilibrium. Figure 8 shows that this equilibrium is not attained in the burned animal until 40 to 60 minutes after the injection. This fact has obvious importance in determining the timing of samples to be taken after the injection of tagged cells for determination of red cell volume in the animals in shock.

DISCUSSION

Reasoning by analogy from the dog experiments, it seems probable that the red cell destruction caused by severe extensive thermal burns in humans is usually of the order of magnitude of 8 to 10 per cent of the original red cell volume. Determinations of the red cell volume in chance burns in humans are now being made in this laboratory. Because no accurate estimation of the red cell volume before injury can be made, it will be necessary to compare the volumes determined after injury in a large series of clinical burns with volumes determined in a large series of normal control patients in order to arrive at an estimate of the red cell destruction caused by the thermal trauma.

If the red cell destruction caused by thermal injury is usually of the order of magnitude of 8 to 10 per cent, it seems unnecessary to replace more than that volume of red cells in the first 48 hours after the burn if the reason for such a plan of therapy is merely the replacement of acutely destroyed erythrocytes. We believe that there may be important dangers in providing the burned patient with more red cells than are acutely destroyed, for the increase in viscosity of the circulating blood may be exaggerated by such therapy.

The implications of this study seem clear. We believe that massive whole blood transfusion therapy of the burned patient is not indicated in the first 48 hours after injury. We favor replacement of the early losses of fluid, protein, and electrolyte caused by thermal injury by means of properly administered plasma and electrolyte solutions. Whole blood may be used in the small amounts required for replacement of estimated red cell losses.

This paper has not dealt with the problems of whole blood replacement in the later days after severe thermal injury. There is no question of the frequent need for liberal use of whole blood transfusions during the phase of infection of the burned area and the phase of preparation of the patient for covering of granulating areas.

SUMMARY

1. The red cell volume of dogs has been determined by using erythrocytes tagged by Cr^{51}. The accuracy of this method is approximately ± 5 per cent of the red cell volume and it is not influenced by the presence of hemolysis.

2. The average maximum destruction of red cells in 8 animals subjected to a 50 per cent body surface immersion in water at 85 degrees C. for 30 seconds was 8 per cent of the red cell volume before injury. The thermal injury produced in these dogs is thought to be comparable to that observed in chance severe burns in humans.

3. The amount of red cell destruction varies with the severity of the thermal injury: 3 animals subjected to a 50 per cent body surface immersion in water at 85 degrees C. for 3 minutes showed an average maximum red cell destruction of 40 per cent of the red cell volume before injury. The injury produced in these dogs is much more severe than that observed in chance severe burns in humans.

4. There is evidence that the even distribution of blood throughout the body is slower after the development of burn shock than in the normal animal.

5. The usual red cell destruction in severe thermal burns in humans is estimated to be about 8 to 10 per cent of the red cell volume before injury.

6. The implications of this finding with respect to the planning of early replacement therapy for patients who have been burned are discussed.

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Fig. 4. Case 3. Left adrenal tumor which weighed 100 grams with extra-adrenal tumor found in immediate proximity.

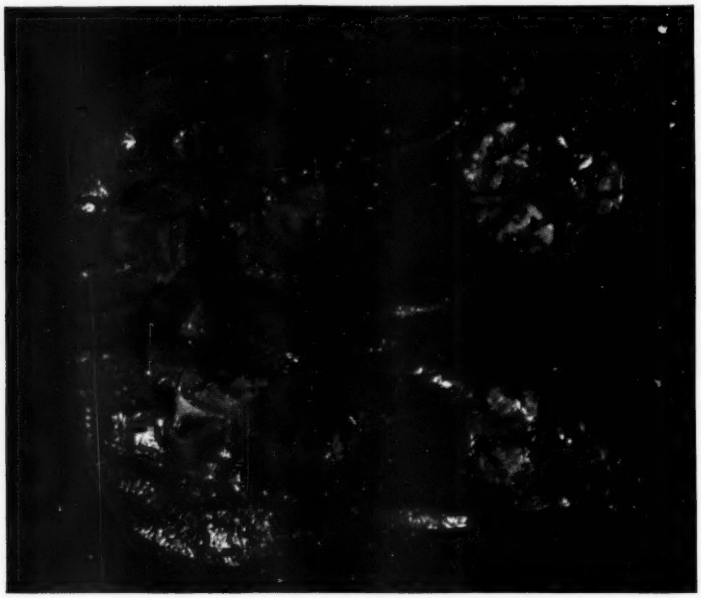

Fig. 5. Case 3. Sagittal section of left kidney with renal cell carcinoma at upper pole. Three small calculi can be seen in lower calyx.

THE SURGICAL MANAGEMENT OF ADRENAL MEDULLARY TUMORS

Report of Four Cases

JAMES E. CONLEY, M.D., F.A.C.S., EINAR DANIELS, M.D.,
ELSTON L. BELKNAP, M.D., and EDGAR END, M.D.,
Milwaukee, Wisconsin

ADRENAL medullary tumors have been encountered in increasing numbers during the past several years due perhaps to a renewed interest in hypertension and the use of drugs for more accurate tumor diagnosis. Certain surgical aspects of the problem such as localization of the tumor, operative technique, and safe conduct during and following extirpation of the tumor require careful consideration. It seemed worth while to report an experience with 4 cases of proved pheochromocytomas inasmuch as the tumors are rare and one must rely on a summation of single case reports or small series for experience in the field. Three of the cases which are to be reported were associated with sustained hypertension and 1 with paroxysmal hypertension. In 1 case, an extra-adrenal as well as an adrenal tumor was encountered. This report concerns these 4 cases with particular emphasis on the surgical aspects of the problem.

LOCALIZATION OF TUMORS

The classic clinical syndrome of paroxysmal hypertension first described by L'Abbe has yielded in importance to sustained hypertension as the more common manifestation of adrenal medullary tumors as described by Green. Certain features associated with sustained hypertension should arouse suspicion and instigate a search for an adrenal medullary tumor. These associated symptoms and signs have been well presented by Smithwick and his associates. The most common manifestations are excessive sweating, vasomotor phenomena, hypermetabolism, normal cold pressor response, postural tachycardia and hypotension, and disturbed glucose metabolism. Any one or more of these clinical features in a patient with hypertension demands investigation for a specific hormonal etiology for the hypertension. It seems unwise to submit all hypertensive patients to the provocative tests with regitine and piperoxan unless a reasonable suspicion exists that a hormonal cause may account for the hypertension (2).

Adrenal medullary tumors are usually small, round, encapsulated, unilateral and reddish-brown in color and, as indicated by Graham, are apparently more common on the right than the left side. Abdominal palpation and massage of flank for provocative blood pressure testing have limited value in localizing the site of a tumor as the majority of tumors are small. Tumors have been found in extra-adrenal locations, most frequently in the abdomen in the lumbar paravertebral region, but they may be found anywhere from organ of Zuckerkandl at the bifurcation of aorta cephalad into chest as shown by Maier and Phillips.

The localization of a tumor when the clinical diagnosis of pheochromocytoma seems evident is difficult but extremely important to the surgeon accepting responsibility for the safe conduct of the patient through extirpation of the tumor. Intravenous and retrograde pyelograms may in some instances be rewarding (Case 1, Fig. 1). However, the abnormalities shown by x-ray examination may be minor variations such as displacement of the upper pole of kidney or deformity of upper calyx. Laminograms of adrenal area may be

From the Department of Medicine and Surgery, Marquette University School of Medicine, Columbia Hospital and Milwaukee Hospital, Milwaukee, Wisconsin.
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Fig. 1. Case 1. Retrograde pyelogram shows displacement of upper pole of right kidney and distortion of renal pelvis.

extremely helpful as in Case 4 (Fig. 6) by actually visualizing the tumor or by contributing negative evidence of normal adrenal glands on one or both sides. We have not employed perirenal air insufflation for contrast visualization because of imminent danger of fatal air embolus or a paroxysmal hypertension crisis inherent in this procedure. Presacral air introduction appears a less hazardous procedure for retroperitoneal contrast visualization.

The accurate localization of an adrenal medullary tumor is important for safe surgery because many of these patients cannot tolerate misdirected surgical exploration either transabdominal or through a posterolateral approach. Accurate localization is important to provide a surgical approach which is direct and which will give ample exposure and thus avoid undue manipulation of the tumor. Positioning on the operating table may be extremely important in paroxysmal hypertensive patients (Case 1) who cannot tolerate the lateral decubitus without severe hypertension being induced.

CASE REPORTS

CASE 1. H. K., a 27 year old housewife, was admitted to Milwaukee Hospital on March 8, 1949 with the chief complaint of nervousness, headaches, easy fatigability and palpitation. She had been well until 1944 when she had the first in a series of episodes of "nervousness." These episodes became more frequent and more severe during subsequent years until 6 months before admission when she became totally incapacitated by almost continuous "nervousness." Episodes were initiated by any minor physical exertion or emotional upset and these episodes consisted of palpitation, throbbing headaches, and nausea and vomiting followed by extreme prostration and profuse perspiration. She was examined by several physicians and a diagnosis of psychoneurosis was made. She was referred to a neuropsychiatrist who saw her several times during a 2 months' period. He concluded that there was an organic basis for her complaints and referred her for hospitalization. No elevated blood pressure had been noted prior to admission.

Family history was irrelevant except for the fact that her father died of diabetes at 63 years of age.

Past history was noncontributory. She had had a dilatation and curettage performed in 1945 for excessive vaginal bleeding. No elevated blood pressure was noted during hospitalization of 3 days.

Physical examination on admission revealed a well developed and well nourished white woman who appeared apprehensive and extremely pale. There was generalized profuse perspiration, and one examining physician described her as "looking as if she just stepped out of a cold shower." Results of eye, ear, nose, and throat examinations were negative. Examination of the neck revealed no masses, tenderness, or stiffness. The breasts were small and no deformity of chest was present. Blood pressure was 130/90; pulse 120. There were no cardiac murmurs, enlargement, or irregularities. The lungs were clear and resonant. The abdomen was soft. There was a well healed, midline suprapubic scar. No masses were palpable. The kidney, spleen, and liver were not palpable. Extremities were essentially negative. Reflexes were active and equal. Weight was 134 pounds.

Laboratory studies showed a red blood count of 4,620,000, hemoglobin 14 grams per cent, white blood count of 9,900 with normal differential count; urinalysis negative; fasting blood sugar 133 milligrams per cent; glucose tolerance test—153 milligrams per cent, 263 milligrams per cent, 226 milligrams per cent, 137 milligrams per cent, 86 milligrams per cent; urea clearance 180 per cent; nonprotein nitrogen 32 milligrams per cent; Kline test negative; cholesterol 190 milligrams per cent; basal metabolic rate plus 14 per cent.

Electrocardiogram showed normal tracing except for frequent extrasystoles and sinus tachycardia; rate 140.

Roentgenograms showed heart of normal size, shape, and configuration. Intravenous pyelogram

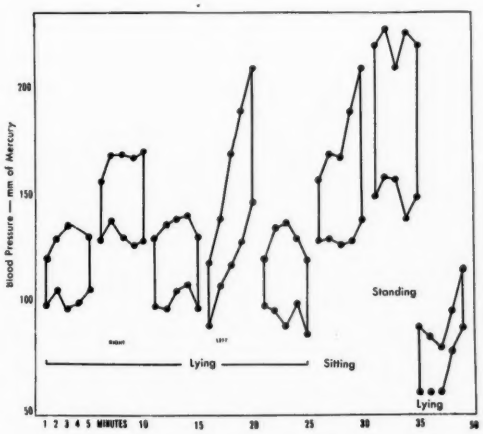

Fig. 2. Case 1. Graph of blood pressure studies showing wide excursion in response to changes of position.

showed deformity of upper renal pelvis with displacement of upper pole of right kidney which was confirmed on retrograde pyelograms (Fig. 1).

Blood pressure studies (Fig. 2) showed: lying 132/102; lying right side 170/132; lying left side 210/148; standing 228/160; lying in prone position 132–152/100–108.

On March 25, 1949 a right adrenal tumor which measured 8 by 7 by 9 centimeters was removed through a posterior approach with patient in prone position. Portions of the eleventh and twelfth rib were resected and the diaphragm was sectioned down to the crus for exposure to avoid trauma in manipulation of the tumor. The patient made an uneventful recovery and she was discharged on the tenth postoperative day. Her blood pressure has been within normal limits and the patient has been well and active.

This case illustrates three of the hazards attendant upon removing an adrenal tumor associated with paroxysmal hypertension. The induction of anesthesia and positioning of the patient may be a hazardous period. This patient had an induction with sodium thiopental in her room and she was maintained during operation in the prone position which, according to our preoperative studies, appeared most favorable. The second hazardous period was during the manipulation of the tumor at which time formidable excursions of blood pressure at high levels were evident (Fig. 3). Following removal of the tumor profound hypotension occurred which in this case was effectively relieved by rapid transfusion

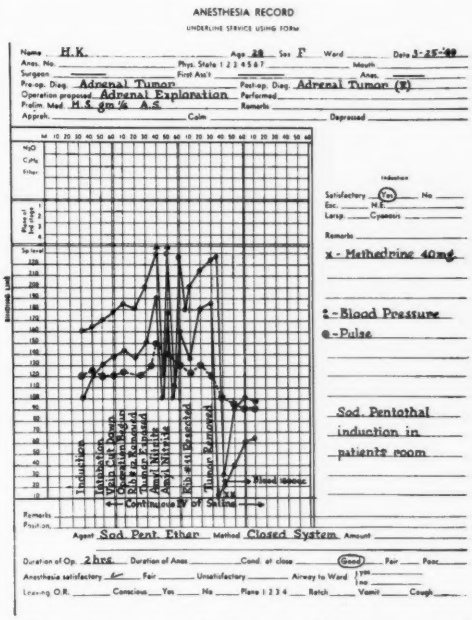
ANESTHESIA RECORD
UNDERLINE SERVICE USING FORM
Name H.K. Age 48 Sex F Ward Date 3-25-49
Anes. No. Phys. Stats 1 2 3 4 5 6 7 Mouth
Surgeon First Ass't Anes.
Pre-op. Diag. Adrenal Tumor Post-op. Diag. Adrenal Tumor (R)
Operation proposed Adrenal Exploration Performed
Prelim. Med M.S. gm.% A.S. Remarks
Approh. Calm Depressed
Satisfactory (Yes) No
Remarks
x - Methedrine 40mg
Blood Pressure
Pulse
Sod. Pentothal induction in patient's room
Induction
Thiopental
Vein Cut Down
Operation Began
Right Kidney Found
Tumor Exposed
Tumor Isolated
Aorta Isolated
Rib Resected
Tumor Removed
Blood above
Continuous IV of Saline
Agent Sod. Pent. Ether Method Closed System Amount
Duration of Op. 2 hrs. Duration of Anes. Cond. at close (Good) Fair Poor
Anesthesia satisfactory Fair Unsatisfactory Airway to Ward Yes No
Leaving O.R. Conscious Yes No Plane 1 2 3 4 Retch Vomit Cough

Fig. 3. Case 1. Anesthesia record of blood pressure and pulse variation in response to manipulation of tumor and following removal of tumor.

of 1,800 cubic centimeters of blood and the vasopressor action of 80 milligrams of methedrine.

CASE 2. H. K., a 43 year old purchasing agent, was admitted to the hospital September 18, 1948 because of acute gastroenteritis which subsided after a few days of hospitalization. The history revealed diabetes and hypertension of about 3 years' duration for which the only treatment had been a low carbohydrate diet. During the past 2 years he had had 4 episodes of dizziness associated with some physical exertion, and the last episode occurred about 6 weeks before admission while driving his car after playing golf. The last attack lasted for 15 minutes and subsided spontaneously when patient rested his head against the car seat. Except for increased perspiration and occasional frontal headache this patient had been well and active.

Physical examination revealed a well developed man, somewhat overweight and in no acute distress. The skin was warm and moist. No undue hyperhidrosis was apparent. His weight was 185 pounds; blood pressure 180/132; pulse 100. Examination was otherwise essentially negative.

Laboratory studies showed: red blood count 4,850,000, hemoglobin, 12.5 grams; urinalysis—specific gravity 1.020, sugar 1 plus, albumin 0, oc-

casional white blood cell in sediment. Fasting blood sugar was 148 milligrams per cent. Glucose tolerance reported was 160 milligrams per cent, 254 milligrams per cent, 284 milligrams per cent, 254 milligrams per cent, 176 milligrams per cent, and 152 milligrams per cent. Basal metabolic rate was plus 42 per cent, plus 24 per cent; nonprotein nitrogen 49 milligrams per cent, 43 milligrams per cent; cholesterol 208 milligrams per cent; phenolsulfonphthalein urine excretion 33 per cent in 15 minutes and 83 per cent in 2 hours. Urea clearance test on two occasions was 180 per cent and 125 per cent.

X-ray examination of the chest showed normal size, shape, and configuration of the heart and normal lung fields. X-ray film of urinary tract by means of intravenous pyelograms showed no abnormality. Laminograms of adrenal area showed normal adrenal visible on right. Electrocardiogram was interpreted as normal except for heart rate of 112.

Blood pressure studies showed extremely variable blood pressure ranging from 178/120 to 120/68 in random blood pressure determination. In postural and cold pressor test the basal lying pressure was 168/128 and standing 142/118. Patient was normoreactor to cold pressor test in lying and standing positions. Piperoxan test with 18.2 milligrams was positive with blood pressure response from 182/128 to 158/110 in 10 minutes.

On October 4, 1948 a right adrenal medullary tumor was removed through a posterior lateral approach with resection of the twelfth rib. The tumor weighed 30 grams and measured 3 centimeters in diameter.

The convalescence was uneventful. The patient was discharged on the tenth postoperative day. Follow-up studies performed 2 months postoperatively showed blood pressure to be 124/86 (lying) and 128/100 (standing). Fasting blood sugar was 110 milligrams per cent with normal glucose tolerance curve.

This case presents a rather typical sustained hypertension and diabetes attributable to a right adrenal medullary tumor. The operation was attended by no untoward blood pressure response and the convalescence was uneventful. A benign operative and postoperative course cannot be anticipated from preoperative observations.

CASE 3.[1] W. O., a 46 year old meat produce superintendent, had known hypertension of 6 years' duration. He saw his local physician for the first time because of left back pain, "pounding in the stomach," and the "jitters." Hypertension was noted. The pressure while under ambulatory treatment varied from 130/80 to 210/110 millimeters of mercury. The patient limited his activities but continued to have frequent "attacks of jitters" which were most severe during the summer of 1948. The tremor was so marked that he dropped a cup of coffee on one occasion. His wife volunteered the information that he "got pale and white as a sheet" following the attacks. He experienced no palpitation, hyperhidrosis, or gastrointestinal disturbances. Blood pressure was never recorded during an attack because the duration was of several minutes and unpredictable. In September, 1948 he had attacks daily which forced him to take an unplanned vacation which provided no relief.

On a routine office visit to his physician in January, 1949 the blood pressure was 236/130. He was admitted to a hospital in another city where, after a period of bed rest and sedation, the blood pressure fell to 190/100. A fasting blood sugar was 196 milligrams per cent and repeated at 132 milligrams per cent. Urinalysis and kidney function tests were within normal limits. Electrocardiogram showed tachycardia (rate 120) and abnormalities consistent with hypertensive cardiovascular disease. There was no cardiac enlargement apparent in the roentgenogram of the chest. He was started on potassium thiocyanate therapy which was thereafter maintained between 8 to 12 milligrams per cent.

In July, 1949 he commenced having painful feet which gradually became worse during subsequent months. The first symptoms were tightness and swelling of both ankles. The toes became so painful that he was unable to spread the toes apart to dry between them after a bath. In December, 1949 roentgenograms of feet showed bilateral osteoporosis, and hospitalization was advised.

In spite of having had daily "attacks of jitters" during September, 1948 with frequent "attacks" during the entire year of 1948, he had been relatively free of "attacks" during 1949, having had only 2 such episodes, one of which occurred in May, 1949 and the other occurred shortly after his admission in December, 1949 for study of hypertension and osteoporosis of the feet.

Family history revealed that his mother died at the age of 42 of a "heart attack." The mother had 2 brothers who died in the fourth decade of life of hypertensive vascular disease. His father at 60 died of heart failure associated with an aortitis. One sister at 43 died of a pelvic tumor. One brother at 44 died, cause unknown. One younger brother was living and well.

Past history was essentially negative except that 6 years previously he had had a traumatic partial amputation of the right ring finger which was sutured under general anesthesia with a very satisfactory functional result. No hypertension was noted during that admission.

Physical examination on admission revealed a well developed and nourished male complaining of inability to walk because of pain and swelling of the lower legs and both feet. Examination was essentially normal except for swelling of both feet and pain on any active or passive motion of the feet and toes. Pulsations were normal in the major vessels of all

[1]Previously reported in part (2).

extremities. Blood pressure was 220/120. Pulse was 100.

Laboratory studies showed on 3 successive days albuminuria and microscopic hematuria; red blood count 4,640,000; hemoglobin 14.2 grams per cent; white blood count 7,200; polymorphonuclears 61 per cent; lymphocytes 35 per cent; sedimentation rate 18 millimeters for 1 hour. The nonprotein nitrogen was 58 on admission but several days later was reported as 41. Blood calcium was 12 milligrams per cent, phosphorus 4 milligrams per cent, and phosphatase 3.3 Bodansky units. Uric acid was 5.6 milligrams per cent. Thiocyanate level was 10 milligrams per cent. Fasting blood sugar was 118 milligrams per cent and 122 milligrams per cent. Basal metabolic rate was plus 16 and plus 22. X-ray studies of chest revealed no cardiac enlargement. Roentgenograms of the skull, spine, and hands showed no abnormalities. Intravenous pyelogram was interpreted as within normal limits except for 3 renal calculi in the left kidney. Laminograms of adrenal area showed normal adrenal gland shadow on the right but none visible on the left.

Roentgenograms of both feet and ankles showed marked bony atrophy of the Sudeck's type. The greatest loss of calcium was in the proximal and distal ends of the long bones of the feet. There was no osteomyelitis, apparent fracture, or evidence of gout visible in the x-ray films. The cause for the acute bone atrophy was not apparent in the x-ray examination. It was thought to be a toxic manifestation of potassium thiocyanate, which therapy was promptly discontinued and daily intravenous procaine therapy begun.

Blood pressure during hospitalization ranged from 300/160 to 180/100. The blood pressure of 300/160 was obtained during one night when he was awakened by the "jitters." The basal blood pressure in the postural and cold pressor test was 178/126; standing 176/120. The patient was not a hyperreactor to the cold pressor test. On sodium amytal sedation blood pressure fell to 132/96. Piperoxan test was negative on 3 different occasions. Histamine 0.25 milligram caused marked rise of blood pressure from 178/120 to 230/148.

Sympathectomy and adrenal exploration on the left were contemplated but deferred during the first admission in December, 1949 because of the bony atrophy in the feet. Intravenous procaine therapy was given with gradual clinical improvement.

He was readmitted for surgery in May 1950, and the following observations were made: The admission blood pressure was 210/112; pulse 88. He had been well and able to work prior to admission with minimal symptoms referable to his feet. Electrocardiogram May 8, 1950 showed changes consistent with left ventricular hypertrophy. Roentgenograms of both feet and ankles revealed some residual bilateral osteoporosis but marked improvement since December, 1949.

Laboratory studies revealed: a fasting blood sugar of 118 milligrams per cent, nonprotein nitrogen was 45, creatinine was 2.0 milligrams per cent; phosphorus 3.8 milligrams per cent; calcium 13.2 milligrams per cent; thiocyanate 2.5 milligrams per cent. Urinalysis showed microscopic hematuria. Phenolsulfonphthalein excretion was 30 per cent in 15 minutes and 82 per cent in 2 hours. Urea clearance was 68 per cent of normal. Sedimentation rate was 24 millimeters per 1 hour. Basal metabolic rate was plus 18 per cent.

TABLE I.—BLOOD PRESSURE DATA IN CASE 3

Date	Lying	Standing	Cold pressor response		Remarks
12-14-49	178/126	176/120	186/132	182/122	Sed. test 132/96
4-6-50	196/116	198/124	208/138	206/132	Histamine test—positive Piperoxan test—negative
5-9-50					Excision of L. adrenal tumor; L. sympathectomy
10-16-50	164/110	160/118	148/116	164/122	
5-4-51	172/112	162/116	168/114	184/126	
7-12-51	166/100	154/110	172/118	174/122	Histamine test—negative Piperoxan test—negative
9-7-51					R. sympathectomy Adrenal exploration
4-21-52	128/90	116/92	130/96	116/98	
4-14-53	122/88	138/100	144/100	148/102	

On May 9, 1950 a left renal and adrenal exploration was performed through the bed of the resected distal 10 centimeters of the eleventh rib. A left adrenal tumor weighing 100 grams which measured 12 by 6.5 by 3.5 centimeters was removed. In addition, an extra-adrenal pheochromocytoma which measured 3.2 by 2.2 by 2.4 centimeters was found near the hilum of the kidney (Fig. 4). An incidental finding was a renal cell carcinoma of the upper pole of the left kidney (Fig. 5) so a left nephrectomy was performed. The addition of ferric chloride (10 per cent) to portions of the adrenal and kidney tumors turned the adrenal tumor a dark green but no effect was noted in the kidney tumor. In addition to the renal tumor, 4 dark reddish-brown smooth stones which averaged up to 0.3 centimeter in diameter were found in the inferior calyces of the kidney. The patient made an uneventful recovery and he was discharged on May 20, 1950.

The patient was well and active without any symptoms following discharge from the hospital. His blood pressure remained somewhat elevated ranging from 160/100 to 184/126 on ambulatory studies. The abnormalities in the electrocardiogram consistent with hypertensive cardiovascular disease persisted postoperatively. The histamine test and piperoxan test were negative.

On September 7, 1951 a right adrenal was explored and found normal. A thoracolumbar sympathectomy (Smithwick operation) was performed

Fig. 6. Case 4. Laminograms at 10 centimeters and 8 centimeters show circular shadow in left adrenal area.

because of persistent hypertension, abnormalities in the electrocardiogram, the bad family history of cardiovascular disease, and the apparent absence of hormonal cause for the hypertension.

Convalescence was uneventful and the blood pressure response to operation during the 18 months' follow-up period has been most gratifying (Table I).

This case presents a sustained hypertension with a paroxysmal hypertension component and adrenal medullary tumors. The hypertension was modified by removal of the tumors. However, some degree of diastolic hypertension persisted. Persistence of hypertension following extirpation of the tumor has been previously reported by Goldenberg and associates. In this patient thoracolumbar sympathectomy provided relief of the hypertension attributable to the secondary mechanism initiated by the pheochromocytoma. The possibility of an additional extra-adrenal tumor seems unlikely in view of the blood pressure response to sympathectomy and absence of clinical evidence of any vasopressor hormonal imbalance observed during the 18 months' follow-up period. Sympathectomy fails to modify the clinical hypertension due to an adrenal tumor.

CASE 4. P. P., a 33 year old salesman, was quite well and active except for mild symptoms which were insufficient to seek medical advice. An elevated blood pressure of 180/110 was noted on routine employment examination 3 years ago which was rechecked and confirmed at 176/108 six months later. Medical advice was sought because of the elevated blood pressure. He was aware of mild dyspnea not related to exertion but which occurred once recently in severe form following bending. He was intolerant of heat and constantly complained of excessive warmth in his home where the temperature was thermostatically controlled at 70 degrees F. He had "always" perspired profusely but when having hair cut on one occasion his barber suggested he see a physician because of the excessive perspiration "which was not normal."

During the 1 year before admission to Columbia Hospital the patient had episodes described as "waves of weakness," which lasted for 1 to 2 minutes and occurred several times each month. Only on 1 occasion had the episode been severe and he "almost lost consciousness." This occurred when leaving a movie theater. He felt profound weakness associated with dizziness and palpitation lasting about 2 minutes, during which time he supported himself against a wall and proceeded on his way after the attack subsided. His physician who had seen him on several occasions because of hypertension performed a regitine test in his office and reported a fall of systolic blood pressure from 206 to 160 millimeters of mercury. Family and past histories were noncontributory. System history was negative. There had been no recent weight loss.

The physical examination on admission to Columbia Hospital on April 1, 1953 revealed a rather apprehensive individual who perspired quite profusely from the face and scalp during the course of the examination. The skin was unduly warm. There was no pallor in the face or in the extremities. Blood pressure lying 206/132, standing 182/140. Pulse rate was 118 in both positions. Peripheral pulsations were readily palpable in upper and lower extremities. Examination of chest, heart, and abdomen revealed no abnormality. Weight was 184 pounds.

Laboratory studies showed: red blood count of 5,050,000, hemoglobin 14.5 grams, white blood count 9,200; sedimentation rate 4 millimeters per 1 hour; nonprotein nitrogen 40 milligrams per cent; fasting blood sugar 127 milligrams per cent, 119 milligrams per cent, 135 milligrams per cent; serum protein 7.42 grams per cent; cholesterol 185 milligrams per cent; urea clearance 110 per cent; basal metabolic rate plus 22 per cent; uric acid 5.6 milligrams per cent; urinalysis—specific gravity 1.018, albumin and sugar negative; phenolsulfonphthalein urine excretion 50 per cent in 15 minutes, 78 per cent in 2 hours. Electrocardiogram was within normal limits; heart rate 92.

X-ray examination of heart showed normal size, shape, and configuration. Intravenous pyelograms were within normal limits. Laminograms of adrenal area (Fig. 6) showed mass in left adrenal area about 5 to 6 centimeters in diameter suggestive of a tumor mass seen best in 10 centimeter level but also visible in 6 and 8 centimeter levels.

Blood pressure studies showed basal blood pressure of 198/128 (lying) and 174/122 (standing). Patient exhibited postural hypotension (Fig. 7) in postural and cold pressor test with technique of Smithwick. Patient was a normoreactor to cold pressor test in both lying and standing positions. On sodium amytal sedation the blood pressure fell to 146/108.

Regitine 5 milligrams intravenously caused a fall of blood pressure from 210/126 to 170/92. Piperoxan 19.6 milligrams caused a fall of blood pressure from 212/132 to 174/104. On the day before surgery the patient was maintained for 2 hours on his right side, and blood pressure varied between 190/120 and 160/118.

On April 14, 1953 a left adrenal tumor was removed through a resected eleventh rib extrapleural and posterolateral approach. The tumor weighed 50 grams.[1] It was roughly spherical and 5 centimeters in diameter. The external surface was smooth and partly covered with scattered segments of adrenal tissue. The consistency of the whole mass was rubbery. A portion of the specimen immersed in 10 per cent ferric chloride solution discolored olive-green promptly.

The operative removal of the tumor was attended by little technical difficulty through the posterolateral approach. Induction of anesthesia was done with 1 cubic centimeter of anectine and 450 milligrams of sodium thiopental. The pulse was irregular for about 3 minutes after the intubation. The initial blood pressure of 240/140 gradually fell to 132/88 following induction and positioning of patient. After commencing the operation the blood pressure fell to 100/72 and it was necessary to maintain a slow drip of methedrine 20 milligrams in 500 cubic centimeters of 5 per cent dextrose in distilled water and a blood transfusion was begun and slowly administered. Following removal of the tumor the blood pressure became imperceptible and remained so during the rapid closure of the wound which required about 15 minutes. A blood transfusion of 500 cubic centimeters was given rapidly and methedrine (20 mgm.) was given intravenously but profound hypotension persisted. The patient was given 2 milligrams of arterenol (levophed R) and a second transfusion of 500 cubic centimeters was begun in spite of an estimated surgical blood loss of 250 to 300 cubic centimeters. The patient was kept in Trendelenburg position while oxygen was administered via endotracheal tube. Frothy blood tinged sputum became evident in the endotracheal tube and nasopharynx which was aspirated, and the oxygen was administered under pressure. Hypotension persisted between 58/40 and 70/50 until phenylephrine (neosynephrine R) 10 milligrams was given intravenously within a 10 minute period. His blood pressure rose to 122/90, pulse 160. A continuous infusion of phenylephrine, 100 milligrams in 500 cubic centimeters of 5 per cent dextrose in distilled water at 60 drops per minute, was maintained. For the subsequent 10 hours the patient required 250 milligrams of phenylephrine, a 500 cubic centimeter transfusion, and 1,000 cubic centimeters of dextran 6 per cent in saline to maintain the systolic pressure between 100 and 120 millimeters of mercury. The patient regained consciousness 2 hours postoperatively. He was rational and co-operative during administration of the massive doses of phenylephrine. Systolic pressure was maintained between 100 and 120 millimeters of mercury by continuous intravenous administration of phenylephrine, 100 milligrams in 600 cubic centimeters of dextrose in distilled water for 36 hours. The dosage was gradually reduced to 5 to 6 drops per minute and it was discontinued on the second postoperative day. Other supportive measures were used such as elastic stockings on legs, low shock blocks beneath foot of bed, and oxygen via intranasal catheter at 4 liters per minute.

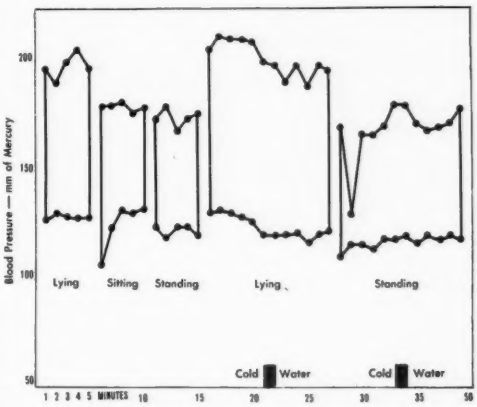

Fig. 7. Case 4. Postural and cold pressor test shows postural hypotension and no reaction to the cold pressor test in the lying and standing positions.

Twelve hours postoperatively the patient was catheterized and 400 cubic centimeters of urine obtained. Fasting blood sugar was 79 milligrams per cent. Red blood count was 5,030,000; hemoglobin 13.5 grams on the first postoperative day. The blood pressure was stabilized after the third postoperative day varying between 140/90 (lying) and 138/94 (standing). His convalescence was uneventful and he was discharged home 12 days after operation.

[1] Tumor specimen was analyzed by paper chromatography and a modification of von Euler's colorimetric method and found to contain: norepinephrine, 3.12 mgm./gm. tumor tissue; epinephrine, 0.96 mgm./gm. tumor tissue. Urinary excretion of catecholamines was equivalent to 600 micrograms norepinephrine, assayed on the cat's blood pressure (reported by Dr. Marcel Goldenberg).

When seen for follow-up examination on May 4, 1953 as an ambulatory patient the blood pressure was 132/88 (lying) and 140/100 (standing). The patient felt fine and remarked that he felt as if the "extra motor" had been removed.

SURGICAL MANAGEMENT

There are three phases of the problem relating to the surgical management of adrenal medullary tumors which must be fully appreciated after the clinical diagnosis and localization of the tumor have been made and the surgeon accepts the responsibility for the safe conduct of a patient through the surgery. Successful management requires the utmost cooperation between anesthesiologist and surgeon. As stated by Huggins, "Adrenal surgery must never be embarked upon lightly." One must anticipate, prevent, and be ready to control operative and postoperative untoward physiologic responses. The three hazardous phases are during induction of anesthesia, manipulation of the tumor, and the circulatory collapse following extirpation of the tumor.

The induction of anesthesia and positioning of the patient for operation may be attended by a serious rise of blood pressure (Case 1) especially in patients in whom a paroxysmal hypertension is present. Such patients must be premedicated and gently managed with the same cautious regard as that in vogue for the management of hyperthyroidism prior to iodine preparation. The induction of anesthesia in some instances may be done to advantage in the patient's room or in a quiet induction room. It is in those patients with severe paroxysmal hypertension associated with interludes of normotension or sustained hypertension that deaths have occurred during anesthesia induction for procedures unrelated to an unrecognized adrenal tumor.

Anesthetic management during surgery is well discussed by Apgar and Papper. The position of the patient on the operating table may be of great importance as some patients cannot tolerate the lateral decubitus position, sometimes employed for the posterolateral approach. Such a patient must be operated upon in the prone position for posterolateral approach or in supine position for transabdominal removal of the tumor.

The second phase of the operation which may evoke a hypertensive crisis is during the manipulation of the tumor. Some tumors (Cases 2 and 3) presented no real problem as the blood pressure showed no perceptible change during manipulation of the tumor. This benign course may be contrasted with the severity of the hypertensive state induced in Case 1 (Fig. 3). The fact that some tumors produce no perceptible change during the gentle manipulation period renders it difficult to assess the merits of various adrenolytic agents recommended for blood pressure control such as regitine, piperoxan, and dibenamine and agents such as amyl nitrite. In this phase of the operation the paroxysmal hypertensives appear to be the more serious offenders. These tumors are extremely vascular and have multiple vascular communications which require individual identification and ligation to control the output of epinephrine and norepinephrine into the blood stream. In some instances in which the blood pressure is alarmingly high the surgeon should withhold further manipulation until the anesthetist has reported a more stable situation existing unless all vascular connections have been ligated. Bleeding may be quite copious during operation but blood transfusion should be used only to replace actual blood loss until after the tumor is removed. Then blood may be administered rapidly to combat the profound hypotension which may become manifested following removal of the tumor.

In the third phase of the operative management when the tumor is removed, profound hypotension must be anticipated. However, hypotension did not occur in Cases 2 and 3. Hypotension may be a compensatory response to the massive infusion of pressor hormones released during manipulation of tumor or may, as apparent in Case 4, be attributable to the withdrawal of the pressor hormones which have for several years sustained a hypertensive state without any support from the sympathicoadrenal system, the mechanism for normal blood pressure regulation. The anesthesiologist must be prepared for rapid infusion of blood, plasma, or dextran and the use of rather massive doses of pressor drugs if the situation demands. A shift from one vaso-

pressor drug to another may be necessary in the event that profound hypotension persists (Case 4). The use of adrenal cortical hormones during this phase seems unwise because of the relatively slow action of cortical hormones. Use of adrenal cortical preoperatively in anticipation of a postoperative profound hypotension is contraindicated because of the salt and water retention which would render the hypertensive state seen during manipulation of the tumor more hazardous. In Cases 1 and 4 blood was administered in excess (1,000 c.c.) of estimated blood loss to provide effective blood volume during this phase. Blood studies done postoperatively showed no evidence of hemoconcentration. One must be guided by the clinical response in employing vasoconstrictor drugs and blood volume supporting measures because in some instances profound hypotension does not develop. This was the experience in Cases 2 and 3.

Persistence of hypertension following extirpation of tumor has been reported by Apgar and Papper and by Goldenberg and his associates. The mechanism of this secondary hypertension poses interesting speculation. In Case 3 bilateral thoracolumbar sympathectomy (Smithwick operation) relieved such a hypertension. This aggressive approach was employed in this case because of the bad family history of vascular disease, the persistence of abnormalities in the electrocardiogram, the relatively high diastolic pressure and the absence of clinical evidence of specific hormonal hypertension. The favorable blood pressure response in this patient seemed to justify this decision.

SUMMARY

Four cases of adrenal medullary tumors associated with hypertension are presented. In 3 of the cases the hypertension was a sustained type.

In 1 patient an extra-adrenal tumor was found adjacent to an adrenal tumor. A modified sustained hypertension persisted following removal of the adrenal medullary tumor. Hypertension was subsequently relieved by thoracolumbar splanchnicectomy.

The cases are presented in detail with a discussion of some aspects of the surgical management of these rare tumors.

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LEIOMYOSARCOMA OF THE STOMACH

Clinicopathologic Study of 40 Cases

RAYMOND G. GIBERSON, M.D., MALCOLM B. DOCKERTY, M.D., and
HOWARD K. GRAY, M.D., F.A.C.S. Rochester, Minnesota

THE stomach is the site of many primary malignant neoplasms. In 98 per cent of gastric malignant disease, the type of tumor is adenocarcinoma, in which the rate of growth is rapid and the results of surgical attack are extremely discouraging. Gastric sarcomas, consisting of lymphosarcomas, leiomyosarcomas, fibrosarcomas and angiosarcomas, make up the remaining 2 per cent. The sarcomas are deserving of a "minority report," however, because they tend to occur in younger patients than do carcinomas, they frequently produce massive hemorrhage clinically, they may present distinctive roentgenologic appearances and finally, in spite of the fact that they may attain a large size, they tend to respond surprisingly well to surgical removal.

Leiomyosarcomas, which make up about 25 per cent of sarcomas affecting the stomach, are the subject of this report.

REVIEW OF THE LITERATURE

Morgagni, in 1762, made what is probably the first documented report concerning a gastric leiomyoma; Virchow, 100 years later, made the first description of a malignant gastric leiomyoma. During the next 40 years, contributions appeared by Fenwick, Cantwell, Baldy, Cappello and Cappello, and Borrmann; these reports were based on surgical and necropsy material and consisted mostly of small series or individual case reports. Although these contributions were scattered, they contained much to clarify the life history of these tumors as they affected the stomach.

Critical studies were made and reported in the early part of the present century by Lecène and Petit, Lofaro, and Flebbe. Forni presented a complete and detailed study of the literature up to 1914.

During the past 25 years, several collective reviews on the subject have appeared. Emphasis has been placed on clinical differential diagnosis based on reports of relatively large series of cases dealing with surgical material. The importance of gastrointestinal hemorrhage as a prominent symptom has been emphasized.

Benign asymptomatic gastric leiomyomas occur rather frequently, as pointed out by Rieniets; malignant change, however, rarely takes place and gastric leiomyosarcomas occur infrequently.

Valuable contributions to the roentgenologic diagnosis of leiomyomatous tumors of the stomach have been made by Allen and Hiebert, Holta, Horsley and Berger, and Mass and Kirshbaum. Schindler and associates, Benedict, and Palmer have considered the diagnostic merits of gastroscopy.

The pathologic features of these tumors have been outlined by Golden and Stout. The criteria for differential microscopic diagnosis have been established by Evans with reference to myosarcomas of the uterus. The importance of mitotic figures in microscopic diagnosis of malignancy in these tumors of the stomach has been emphasized by Golden and Stout, Laube, and Melnick.

MATERIALS AND METHODS

The records used in this study were taken from the surgical files of the Mayo Clinic from the years 1907 to 1950, inclusive. The review included records in all cases filed as leiomyosarcomas, gastric fibrosarcomas, angiosarcomas, and spindle cell sarcomas. All the gross

Abridgment of thesis submitted by Dr. Giberson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

From the Mayo Foundation (Dr. Giberson, Fellow in Surgery), and the Divisions of Surgical Pathology and of Surgery, Mayo Clinic, Rochester, Minnesota.

specimens had been preserved in 10 per cent solution of formalin; these were available for review in addition to a large number of slides prepared at the time of the original diagnosis. Recourse was had to necropsy material only in cases in which the patient died after operation. Forty-three supposed gastric leiomyosarcomas were available for study after a preliminary survey; 4 of these were considered to be benign and were excluded from our series.

Benign gastric leiomyomas removed surgically during the same period were reviewed next. One of these lesions was transferred from the benign to the malignant group after this study. Therefore, our final selection embraced 40 cases of gastric leiomyosarcoma in which surgical exploration and indicated surgical treatment had been done.

Each gross specimen was inspected and studied. Representative blocks of tissue were selected and placed in fresh 10 per cent solution of formalin. These were sectioned on a freezing microtome, stained with hematoxylin and eosin, and mounted permanently on glass slides. It has been demonstrated that myoglial fibrils occasionally may be seen if fresh tissue is placed immediately in Zenker's fluid and stained with Mallory's phosphotungstic acid hematoxylin. Special stains were not employed in our study, however, since the tissues in these cases had been in formalin for some time and since these stains had not proved helpful in other similar studies. Pathologic and clinical features were tabulated and analyzed.

CLINICAL FEATURES

Age and sex incidence. This series included 17 females and 23 males (Table I). The youngest patient of each sex was 10 years of age. The oldest woman was 73 and the oldest man 70 years of age. About half (19) of the patients were between 40 and 59 years of age, inclusive. The average age of the females was 45 and of the males 46.5 years. The average age of all patients was 45.7 years. Eight were less than 30 years of age.

Symptoms. The complaints presented were chiefly referable to (1) the presence of an abdominal mass, (2) gastrointestinal bleeding, and (3) abdominal distress.

TABLE I.—AGE AND SEX INCIDENCE IN 40 CASES OF GASTRIC LEIOMYOSARCOMA

Age, years	Males	Females	Total
10–19	2	1	3
20–29	4	1	5
30–39	1	4	5
40–49	5	5	10
50–59	5	4	9
60–69	5	1	6
70–79	1	1	2
Total	23	17	40

The presence of an abdominal mass noted by the patient was one of the presenting complaints in 12 cases. The average length of time during which a tumor was known to have been present was 18.2 months. The shortest time was 4 days and the longest 7 years. One patient had known a mass to be present for 3 years with little change until 6 months prior to registration at the clinic, when a rapid increase in size had been observed.

Gross bleeding from the gastrointestinal tract had been noted by 19 patients. Three additional patients had experienced symptoms of chronic loss of blood without gross evidence of gastrointestinal hemorrhage. Of these 22 patients, 2 gave hematemesis as the presenting complaint. When first seen at the clinic, a 10 year old boy gave a 2 year history of severe anemia, for which splenectomy had been done without improvement. Gastrointestinal bleeding was associated with active ulceration of the mucosa overlying the tumor in 15 patients.

Abdominal distress had been noted by 30 patients; in 13 of these, abdominal pain was a prominent complaint. Pain, when present, was experienced most often in the left upper quadrant or epigastric region. In some it was severe and constant, in others it was colicky in nature. The pain had been present for a relatively short time in most instances, the longest duration being recorded in a patient who had experienced recurrent attacks of epigastric pain for 1 year. Ten patients gave typical "ulcer" histories, with relief of abdominal distress induced by food and alkali. Nausea and vomiting were not prominent features and symptoms of pyloric obstruction were not noted.

Fig. 1. Large (18 by 16 by 9 cm.) exogastric leiomyosarcoma. The neoplasm was attached to the greater curvature and extended into the greater omentum. Note the characteristic nodular lobulated appearance. The cut surface shows multiple regions of degeneration.

Physical examination. Three patients appeared acutely ill, with signs indicative of severe loss of blood. Pallor was noted in 11 patients. Obvious signs of loss of weight were present in 20 patients; the average loss was 16.1 pounds (about 7.3 kgm.) and 1 patient had lost 50 pounds (22.7 kgm.). An abdominal mass was palpable in 19 patients; as previously noted, the tumor had been found by 12 of these patients. Six lobulated tumors in the left upper quadrant were mistaken for enlarged spleens. The mass, usually in the epigastrium or the left upper quadrant, was described most frequently as being movable, firm, and slightly tender. Abdominal tenderness was noted in 10 patients but was not of great degree in any. Tenderness was generalized in 2 patients but in the remainder it was in the epigastrium or the right upper quadrant.

TABLE II.—LABORATORY FINDINGS IN 40 CASES OF GASTRIC LEIOMYOSARCOMA

	Cases	Values		
		Average	Lowest	Highest
Hemoglobin	40	10.4 gm. per 100 c.c. of blood	5.1 gm.	15.2 gm.
Erythrocytes	34	3,800,000 per cu. mm. of blood	2,020,000	5,200,000
Leucocytes	37	7,300 per cu. mm. of blood	3,800	11,100
Erythrocytic sedimentation rate	14	34 mm. in first hour (Westergren)	4	90 mm.
Gastric acidity	23	52 combined and 37 free units	No free HCl	86 combined and 74 free units

Laboratory tests. Laboratory findings of significance are listed in Table II. Special hematologic examinations of blood smears were carried out in 13 patients; 8 displayed hypochromic microcytic anemia and 5 were normal. In 18 of the patients whose histories were reviewed, values for hemoglobin were less than 10 grams per 100 cubic centimeters of blood.

Roentgenologic examination. Roentgenologic studies were not done in 6 patients, since no gastric lesion was suspected. Nothing abnormal was discovered in 4 of those patients who were examined. Gastric leiomyomatous tumors were thought to be present in 3 patients and malignant tumors of some nature in 7. Extragastric masses were noted in 6 patients. In the remaining patients, gastric tumors of indeterminate nature were diagnosed. The various roentgenologic signs supporting these diagnoses are listed as follows: ulceration in 13 cases, extragastric mass in 6, polypoid intragastric mass in 10, intramural or subserosal mass in 7, fistulous tract in 3, no abnormalities in 4 cases.

Gastroscopic examination. Gastroscopic procedures were done on 3 patients. The appearance of Menetrier's disease was reported in 1 of these. In another, the diagnosis of leiomyosarcoma was made by gastroscopic examination. The report in this case read as follows: "The patient has a large tumor which is growing from the anterior wall of the stomach below the cardia and projecting into the lumen of the stomach. The surface is smooth over most of the tumor, but toward its apex are several small areas of pitting, one of which appears to be perforating into the tumor. The gastroscopic picture suggests a large leiomyoma or a leiomyosarcoma involving the anterior wall of the stomach." In the third patient, results of gastroscopic examination were indeterminate.

PATHOLOGIC FEATURES

The average size of 37 tumors was 9 by 8 by 6.3 centimeters. The largest was 20 centimeters and the smallest 3.5 centimeters in diameter. The only tissues available in 3 cases were specimens taken for biopsy.

The neoplasms varied greatly in shape but all had a characteristic lobulated and nodular appearance (Fig. 1). In most instances, it was impossible to determine from the specimen whether the tumor was intragastric, intramural, or exogastric. Three tumors were dumbbell in shape and 5 were pedunculated.

The growths were firm and rubbery in consistency except when degenerative changes had taken place. The cut surfaces of the fresh specimens were mahogany brown, interspersed with yellow. When the specimen was preserved in formalin, the cut surface was pink. Necrotic changes were noted in 18 tumors. Seven had undergone cystic changes and 2 were filled with necrotic fluid and old blood.

Ulceration of the gastric mucosa overlying the tumors was noted in 23 specimens, and evidence of healed ulceration was present in 7 others (Fig. 2). Multiple zones of ulceration were seen in 5 specimens. The ulcers varied considerably as to depth and width; in 1 case, the ulcer was 4 centimeters in diameter. Deep sinus tracts extended into the central portions of the tumors in 2 cases.

The location of the neoplasms in relation to the stomach is depicted in Figure 3. Sixteen tumors were located on the posterior wall, while the remainder were situated on the anterior wall or one of the curvatures. No tumor occurred in the region of the pylorus or the upper part of the fundus.

Microscopic features. The cells were typically spindle-shaped, like those of normal smooth muscle (Fig. 4). A moderate amount of cytoplasm was present; this stained well with eosin. Nuclei were oval and were located near the center of the cells. Giant cells were seen in regions of degeneration; in these cells, the nuclei were large, irregular in shape, and hyperchromatic, with a small amount of eosinophilic cytoplasm. The presence of giant cells was noted in 8 tumors.

The arrangement of the cells varied, but in general they tended to line up along the long axes (Fig. 5). This polarity, which was most extensive in lesions of low grade malignancy, was suppressed in tumors of lesser degrees of differentiation. Loss of polarity was a prominent feature in 9 tumors. The nuclei of the cells tended sometimes to be arranged in palisades; this particular feature was also present in 9 tumors (Fig. 6).

Mitotic figures were noted in all 40 tumors. At least 1 mitotic figure per high power field was present in 25 tumors; in 16 of these, 2 or more mitotic figures per field were found. In the remaining 15, mitotic figures were few in

Fig. 2. Resected portion of stomach containing a leiomyosarcoma. Note the elevated bridges of mucosa at the edge of the tumor, typical of a submucosal neoplasm. The deep mucosal ulceration is characteristically seen overlying leiomyomatous tumors, both benign and malignant.

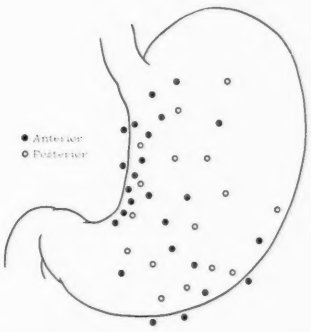

Fig. 3. Location of the 41 gastric leiomyosarcomas in the 40 patients in this series. Note absence of tumors occurring in the region of the upper part of the fundus and the pylorus.

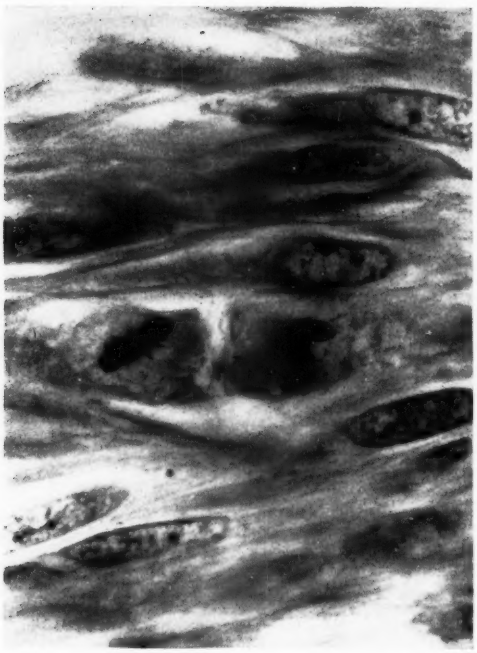

Fig. 4. Gastric leiomyosarcoma. Note cell undergoing division. The spindle shape of the cells is well demonstrated, as are the oval nuclei. Hematoxylin and eosin, ×1,300.

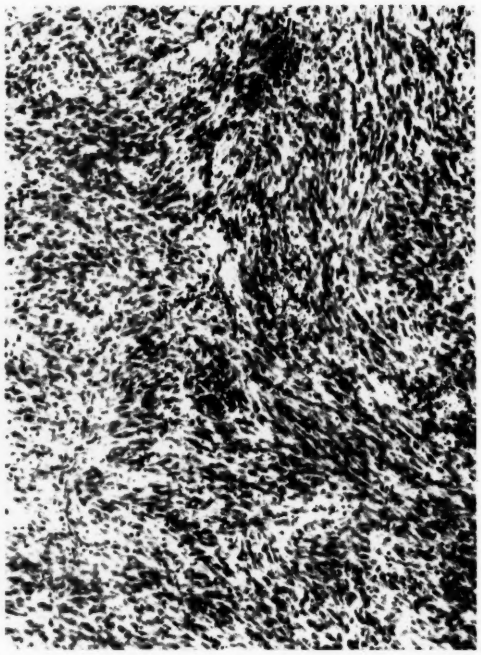

Fig. 5. Metastatic nodule in the greater omentum arising from a primary gastric leiomyosarcoma. Hematoxylin and eosin, ×100.

number; only an occasional dividing cell could be seen in several. Pathologic forms were encountered infrequently.

The stroma varied in amount but in most cases there was little. When present it appeared as an eosinophilic hyaline material, being more abundant in some regions than in others. An open myxomatous arrangement of the cells was seen in edematous parts of the tumors. Zones of necrosis were noted microscopically in 18 tumors, with loss of cellular structure and evidence of hemorrhage in many fields.

The cellularity was graded on a basis of 1 to 4, in which 1 indicated that seen in a benign leiomyoma and 4 indicated the most extensive degree of cellularity. Two tumors were graded 1, 17 were graded 2, 18 were graded 3, and 3 were graded 4.

The pleomorphism was also graded 1 to 4, in which grade 1 showed the least and grade 4 the greatest variation from normal. Seventeen were graded 1, 19 were graded 2, and 4 were graded 3.

The malignancy of the tumor was graded on a basis of 1 to 4, after the method of Broders. Seventeen were graded 1, 16 were graded 2, and 7 were graded 3. No grade 4 lesion was encountered.

Characteristics of metastasizing tumors. Eighteen tumors metastasized. In 6 cases, spread was evident at the time of operation, while in the other 12, evidence of metastasis appeared at a later date. The liver was involved grossly in 4 patients at the time of operation; 2 additional patients exhibited peritoneal invasion. In 3 of these 6, the lymph nodes were affected by direct extension. In no instance did tumors spread to lymph nodes other than by direct extension. No metastatic lesions were noted outside the abdominal cavity.

A tumor recurred or a new tumor presented itself after 23 years in 1 instance. In this case,

a low grade leiomyosarcoma was removed by partial gastric resection when the patient was 10 years of age; 23 years later, further resection was done for a tumor in the lower portion of the gastric remnant. This tumor had the same histologic picture as that removed earlier.

The microscopic appearances of the metastasizing tumors were studied in an effort to discern any special features (Table III). Increased cellularity was present in all the metastasizing tumors, although not notably in some cases. Pleomorphism was a feature in all 18 but it was extensive (grade 3) in 2 only. At least one mitotic figure per high power field was found in all but 2 of the metastasizing tumors. In these 2 tumors, 1 mitotic figure was present in every 3 to 5 fields. The grade of malignancy was 2 or more in all metastasizing lesions.

The features in the remaining 22 cases, in which no metastasis occurred, were studied and compared with the group of cases in which metastasis was present (Table IV). The most striking feature of the lesions that did not metastasize was the scarcity of mitotic figures. Rare or occasional dividing cells were seen in 13 of these cases. Nine tumors showed 1 or more mitotic figures in each high power field but 4 of the patients who had such tumors died early of other causes or have not been followed long enough to allow evaluation of the metastatic capabilities of the tumors. The tumors that did not metastasize were slightly less pleomorphic and less cellular as a group than the metastasizing examples, but the differences were not great. The average grade of malignancy was less than in the metastasizing group; 17 of the 22 nonmetastasizing tumors were graded 1, whereas no metastasizing tumor was graded 1. Four of the tumors were graded 2; in 3 of these latter cases, the follow-up was of an insufficient length of time to allow evaluation of their ultimate metastatic potentialities. The final patient in this group had a grade 3 neoplasm; the patient was well 3 years after operation.

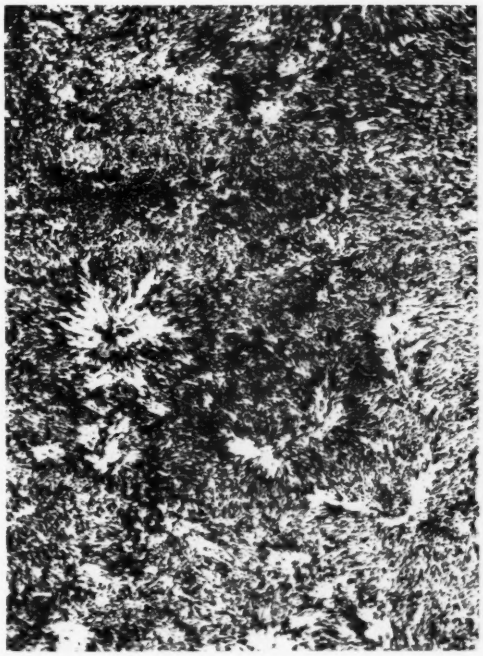

Fig. 6. Palisading of nuclei in leiomyosarcoma. This neoplasm metastasized to the liver and peritoneum. Hematoxylin and eosin, ×60.

TREATMENT AND PROGNOSIS

Surgical exploration was carried out in all cases. Partial gastrectomy was done on 22 patients and total gastrectomy on 3. The tumor was removed by local excision in 12 instances; 1 of these tumors was excised by cautery and another was removed by the transgastric route. Abdominal exploration with biopsy of the tumor only was carried out on 3 patients.

Roentgen therapy was administered additionally to 5 patients, 2 of whom had undergone biopsy only. Two received roentgen therapy only after recurrence of the tumor became manifest. Radium was inserted into the bed of 1 tumor after local excision from the posterior gastric wall; supplementary roentgen treatment was given later in this case. One patient whose tumor recurred 6 months after local excision was treated by means of nitrogen mustard.

Two hospital deaths occurred among the 40 patients in this series, giving a mortality rate of 5 per cent. In the calculation of survival

TABLE III.—SUMMARY OF 18 CASES OF METASTASIZING GASTRIC LEIOMYOSARCOMA

Case No.	Microscopic features				Treatment†	Survival time
	Cellularity, grade	Pleomorphism, grade	Mitotic figures*	Malignancy, grade (Broders)		
1	3	2	2–3	2	L.E.	9 months
2	3	3	1–2	2	P.G+R.	9 months
3	2	2	2	2	P.G.	7 months
4	3	2	4–5	3	L.E.	6 years
5	3	2	5–6	3	P.G.	2 years and 10 months
6	2	2	Occas.	2	B.+R.	6 years
7	3	1	1	2	T.G.	3 years
8	3	1	Occas.	3	P.G.	1 year and 4 months
9	3	2	1	2	L.E.+radium+R.	3 years and 4 months
10	3	2	2	3	B.	1 month
11	2	1	2	2	L.E.	1 year and 8 months
12	3	1	2	2	T.G.	4 days
13	4	2	2	2	P.G.	4 months
14	3	2	3–4	2	L.E.	1 year
15	2	2	2–3	3	T.G.	8 months
16	3	3	1	3	B.+R.	9 months‡
17	2	1	5–6	2	L.E.+nitrogen mustard	1 year
18	4	2	1	2	P.G.+R.	4 years

*Numbers refer to numbers of mitotic figures per high-power microscopic field.
†L.E.—local excision; P.G.—partial gastrectomy; B.—biopsy; T.G.—total gastrectomy and R.—roentgen therapy.
‡Death by suicide.

rates, the hospital deaths are excluded. January 1, 1952, was considered as the date of inquiry; 10 patients were operated on since 1946 and thus must be excluded in the calculation of the 5 year survival rate. In the remaining group of 28 cases, 2 were untraced and 26 were eligible for use in determination of the 5 year survival rate; among these 26 patients, 14 (53.8 per cent) lived 5 or more years after operation.

The terminal stages of gastric leiomyosarcoma featured cachexia. Three of the patients in this series died of intestinal obstruction. Ascites frequently developed in the late stages of the disease.

COMMENT

The age and sex distribution in this series, as in those series reported in the literature, shows a nearly equal sex incidence and an occurrence most frequent between the ages of 40 and 59, inclusive. Eight of the patients, however, were less than 30 years of age, which is in contrast to the relatively small percentage of gastric carcinomas occurring in this age group.

The symptoms depend on the size of the tumor, the rate and direction of its growth and whether ulceration of the overlying mucosa is present. Bleeding, a prominent feature, is often severe and recurrent; melena or hematemesis or both may be present and anemia sometimes is pronounced in the absence of any other evidence of hemorrhage. Lahey and Colcock, in a report of 7 cases, found an average value for hemoglobin of 63 per cent. The average value for hemoglobin in this series was 10.4 grams per 100 cubic centimeters of blood. Vague and variable symptoms of indigestion recalled those due to peptic ulcer or carcinoma, the pain yielding for a time to an ulcer regimen; this was noted also by Horsley and Berger. The presence of an upper abdominal mass was noted by the patients in 40 per cent of reported cases and in 30 per cent of those in this series.

TABLE IV.—SUMMARY OF 22 CASES OF NONMETASTASIZING GASTRIC LEIOMYOSARCOMA

Case No.	Microscopic features				Treatment†	Date of operation	Follow-up
	Cellularity, grade	Pleomorphism, grade	Mitotic figures*	Malignancy, grade (Broders)			
1	3	2	Rare	1	P.G.	4-8-13	Dead April, 1922; myocardial infarction
2	3	2	2-3	1	P.G.	8-9-19	Dead in weeks; no details
3	1	1	Occas.	1	L.E.	12-15-28	Well Dec., 1950
4	2	1	1	1	P.G.	4-13-29	Well Dec., 1950
5	2	1	Rare	1	P.G.	5-27-35	Well June, 1948
6	3	2	3-4	2	P.G.	2-19-36	Dead Aug., 1938; cancer of cecum
7	2	1	Rare	1	P.G.	9-21-38	Well Dec., 1950
8	3	3	Rare	1	P.G.	10-7-38	Well Mar., 1951
9	2	2	Rare	1	L.E.	5-13-40	Died in operating room; myocardial infarction
10	3	1	Occas.	1	P.G.	6-14-40	Well Dec., 1950
11	2	1	Occas.	1	P.G.	12-10-41	Well June, 1946
12	2	1	2-3	1	L.E.	2-20-43	Well Jan., 1952
13	2	1	Rare	1	L.E.	8-26-43	Well Feb., 1951
14	4	1	Rare	2	P.G.	6-26-43	Well June, 1950
15	1	1	Rare	1	P.G.	8-16-46	Well Jan., 1951
16	3	3	3-4	3	P.G.	1-17-47	Well Dec., 1950
17	2	2	Rare	1	L.E.	4-22-47	Well Jan., 1951
18	2	2	1	1	P.G. (twice)	7-24-24 and 9-19-47‡	Well Jan., 1951
19	3	2	1	2	P.G.	9-13-48	Well Dec., 1950
20	2	1	Occas.	1	L.E.	6-4-49	Well Mar., 1950
21	2	1	1	1	P.G.	12-3-49	None
22	2	2	2-3	2	P.G.	2-2-50	None

*Numbers refer to numbers of mitotic figures per high-power microscopic field.
†P.G.—partial gastrectomy and L.E.—local excision.
‡Recurrence after 23 years.

Roentgenologic examination is the most valuable single diagnostic aid; it reveals the presence of an operable lesion in a great percentage of cases. Ulceration of the gastric mucosa over a mass protruding into the stomach with the presence of a deep sinus tract extending into the tumor is highly suggestive of malignant leiomyoma; these findings indicate degeneration and necrosis of the center of the tumor (Fig. 7). Such tracts also may be seen in benign leiomyomas, however.

Gastroscopy is sometimes beneficial as a diagnostic procedure; this procedure helped to make the diagnosis of leiomyosarcoma in 1 case in our series. However, the method does have definite limitations. Biopsies made with the aid of the gastroscope and showing benign leiomyoma do not exclude the possibility of malignant disease in other portions of the tumor.

The differential diagnosis of these tumors is important. They should be separated from the lymphosarcomas since they are not radiosensitive, whereas the lymphomatous lesions are. They may, however, like lymphosarcomas, present large tumors that are operable and curable.

Carcinoma of the stomach usually pursues a far more rapid course than does gastric leiomyosarcoma; when a palpable mass is present in the former, it is likely to be fixed and the patient usually is cachectic. The duration of symptoms before medical advice was sought in a series of gastric myosarcomas stud-

Fig. 7. Large (10 by 10 by 8 cm.) gastric leiomyosarcoma located on the lesser curvature in a 17 year old boy. Note regions of mucosal ulceration and presence of a barium-filled sinus. There were 3 to 4 mitotic figures per high power field; several lymph nodes were involved by direct extension. The patient was living and well 5 years after removal by means of partial gastrectomy.

ied by Holta was 3½ years. In this series it was 2.9 years. The symptoms of anorexia and digestive distress usually are less extensive in leiomyosarcoma than in carcinoma, it being not uncommon to see patients partaking fairly well of food even in the presence of extensive involvement of the stomach by a leiomyosarcoma. Massive hemorrhage is more frequent in patients who have leiomyosarcoma, and pyloric obstruction is less likely to develop.

It is difficult to separate the intragastric type of lesion from other polypoid lesions of the stomach, and it may be impossible to differentiate clinically the infiltrating variety of leiomyosarcoma from linitis plastica types of carcinoma or sarcoma. Horsley and Berger were of the opinion that a fairly long history, with moderate debility, a palpable mass and roentgenologic evidence of deformity caused by pressure on the gastric wall favor the diagnosis of leiomyosarcoma.

It is extremely difficult to differentiate clinically leiomyosarcomas from benign gastric leiomyomas. The differential diagnosis is based chiefly on the circumstances that the malignant form grows expansively, breaks through its natural boundaries and is more likely to undergo degenerative changes, with necrosis, deep ulceration, and the formation of sinus tracts.

In the absence of metastasis, the malignant nature of the tumor may not be suspected until after microscopic examination. It would appear from the above study, and it has been substantiated by work elsewhere, that the only reliable criterion of malignancy is the presence of mitotic figures and that, in general, the likelihood of recurrence or metastasis is related directly to the number of mitotic figures present. When mitotic figures are associated with pleomorphism and great cellularity, the tumor is almost certainly capable of metastasizing. The reverse is not true, however, since 2 of these tumors metastasized despite the presence of only occasional mitotic figures and moderate degrees of cellularity and pleomorphism. Melnick has reported a case of gastric leiomyoma with a benign histologic appearance in which gross hepatic metastasis was present; thus, it appears that a tumor, adequately studied histologically and regarded as being benign, may on occasions prove its malignant character by its subsequent course.

Gastric leiomyosarcoma spreads slowly and its secondary lesions usually are limited and localized in extent. The liver is the most common site of metastasis, although peritoneal spread is seen sometimes. That lymph nodes rarely may be involved is proved by reported cases; no evidence of spread to lymph nodes was found in our series except by direct extension. Schindler and associates found metastasis in 15 per cent of their collected cases. Cameron and Breslich reported metastatic lesions in 20.5 per cent of a series of 39 cases, in only 1 of which were metastatic lesions found beyond the abdominal cavity. Metastasis was present in 18 of our cases, as already mentioned.

It was difficult to evaluate the relative merits of the three surgical procedures employed. In 6 of the 18 patients who had metastatic le-

sions, the spread already was present at the time of operation. Among the 12 patients who later exhibited evidence of metastasis, 5 had undergone removal of the tumor by local excision, 5 by partial gastrectomy, and 2 by total gastrectomy.

Little evidence could be adduced that therapy with roentgen rays, radium or nitrogen mustard altered the course of the disease, although 1 patient who received roentgen therapy lived 6 years despite the presence of known metastasis in the liver. None of the patients living 5 years after removal of the tumor had received roentgen therapy.

It is agreed generally that the surgeon should attack these tumors boldly. Even in the presence of metastasis, removal of the primary tumor may give years of life. Surgical intervention is the only method of treatment that is worth while, since these tumors are radioresistant. Schindler and co-workers mentioned a case in which exploration was done before and again after radiotherapy; no apparent beneficial effect had been produced by the radiation. Watson has stressed the point that these tumors, particularly the exogastric type, may appear inoperable, whereas actually a good result from surgical removal may be obtained.

SUMMARY AND CONCLUSIONS

A study was made of 40 cases of leiomyosarcoma of the stomach in which surgical removal of the tumor had been done at the Mayo Clinic. This gastric tumor is relatively rare; only 135 cases have been reported in the literature.

Cardinal symptoms noted were: (1) abdominal distress, (2) gastrointestinal hemorrhage, and (3) the presence of an abdominal mass.

The most characteristic physical finding was the palpation of an abdominal mass. Evidence of chronic loss of blood was noted in many patients and the average value for hemoglobin in the series was 10.4 grams per 100 cubic centimeters of blood.

Roentgenologic studies indicative of a submucosal gastric tumor with ulceration of the overlying mucosa and the presence of a fistulous tract leading into the tumor are suggestive of leiomyosarcoma.

These tumors are firm and rubbery unless they are degenerated; ulceration was present in 23 cases. The typical microscopic picture is that of smooth muscle, with increased cellularity, pleomorphism and the presence of mitotic figures.

Gastric leiomyosarcomas spread principally by way of the blood stream and invade primarily the liver. The only method of spread to lymph nodes in this series was by direct extension. Nineteen tumors metastasized or recurred. The capability of these tumors to metastasize was correlated with the presence of mitotic figures, the degree of cellularity, and the extent of pleomorphism of the cells.

The treatment of choice is surgical removal of the neoplasm, even in the presence of metastasis. One patient lived 6 years despite known metastasis in the liver. Roentgen therapy was not found to be beneficial.

The 5 year survival rate among 26 patients whose follow-up studies warranted such calculation was 53.8 per cent.

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GRANULOMATOUS OR GIANT CELL THYROIDITIS

A Clinical and Pathologic Study of Thirty-seven Patients

STUART LINDSAY, M.D., and MORRIS E. DAILEY, M.D., San Francisco, California

GRANULOMATOUS or giant cell thyroiditis is characterized by clinical evidences of subacute, nonsuppurative inflammation of the thyroid gland and by a histologic spectrum of acute, subacute, and chronic inflammation with multinucleated giant cells and fibrosis. Synonyms for this disease are acute thyroiditis, acute nonsuppurative thyroiditis, subacute thyroiditis, pseudotuberculous thyroiditis and de Quervain's thyroiditis. The chronic stage has been designated by some authors as Riedel's struma. Although this disease appears to be a distinct entity, a completely satisfactory name for the process has not yet been devised.

The present study is concerned with 37 patients having this form of thyroid disease. Twenty-five of the patients had thyroidectomy, and their glands were examined histologically. The majority of the patients were seen by members of the Thyroid Clinic of the University of California Hospital.

The purposes of this report are: (1) to describe the distinctive course of this disease and to make clinical correlations which may aid in diagnosis; (2) to describe and illustrate the characteristic pathologic lesions; (3) to stress the clinical and pathologic differences between this type of thyroiditis and "Hashimoto" and "Riedel" thyroiditis; and (4) to discuss various views regarding the etiology, pathogenesis, and treatment.

INCIDENCE

From 1920 through 1952, thyroidectomies were performed on 7,263 patients at the University of California Hospital. Of these, 23 patients (0.31 per cent) had granulomatous or giant cell thyroiditis, 220 patients (3.0 per cent) had proved Hashimoto thyroiditis, and 2 patients (.027 per cent) had Riedel thyroiditis. There has been no significant change in the incidence of granulomatous thyroiditis in each of the three decades from 1920 to 1950. Since 1944, the majority of our patients with granulomatous thyroiditis have been treated medically.

From the Departments of Pathology and Medicine and the Thyroid Clinic, University of California School of Medicine, San Francisco. Supported by the Cancer Institute Research Fund and by Cancer Research Funds of the University of California School of Medicine, San Francisco, California.

ETIOLOGY

That the thyroid epithelial injury is probably not bacterial is indicated by reports of negative bacterial cultures of these thyroid glands. Rienhoff believed that infection spread from the pharynx to the thyroid gland through lymphatic channels. Results of routine cultures on a number of glands in our series have been negative. Furthermore, antibiotics appear to have no effect on the disease. Schilling believed that this thyroid disease was produced by bacterial toxins originating in the pharynx since, in many of his patients, pharyngitis preceded the onset of thyroiditis.

De Courcy has suggested that these thyroid lesions are secondary to perithyroiditis, accompanied by lymphangitis extending into the gland. He believed that thyroid atrophy and fibrosis in this type of thyroiditis are the result of intimal fibrosis of the thyroid blood vessels. We have observed such vascular lesions but have found them only in the later fibrous stages of the disease. They closely resemble the thickened blood vessels seen in other chronic inflammatory sites such as chronic peptic ulcer and chronic pyelonephritis and are undoubtedly secondary to the chronic inflammatory reaction. In a recent study Chesky and his co-workers indicated that alterations of the colloid composition initiate the proliferative inflammatory process in thyroiditis and likened the reaction to that of chemical inflammation. Apparently Hashimoto and subacute thyroiditis were not differentiated in this study which has not been

confirmed. Fraser and Harrison believed that the epithelial injury might result from viral invasion in view of the prodromal constitutional symptoms, the diminished or absent uptake of I^{131} and the immediate clinical response to methylthiouracil, which these authors believed to be an antiviral agent. We have examined the thyroid glands in our series for nuclear or cytoplasmic inclusion bodies and have found none.

The focal nature of the disease which initially involves the epithelium, the characteristic successive involvement of thyroid follicles, and the febrile clinical course have suggested to us that the lesions might be reactions of hypersensitivity. We are investigating that possibility at present.

In 9 of the 37 patients in our study, transient enlargement of the thyroid gland had occurred previously, usually during adolescence. Apparently, however, no relation existed between the previous thyroid disease and the thyroiditis.

The variability of the clinical course of this disease suggests that more than one etiologic agent may cause the original thyroid epithelial injury. We have observed identical proliferative reactions in scattered follicles in colloid goiters (15) and in a gland irradiated from I^{131} (7). Intrafollicular proliferation of mononuclear cells and multinucleated giant cells associated with loss of colloid was identical in these instances to the reaction observed in granulomatous thyroiditis.

CLINICAL OBSERVATIONS

Various reports have described the salient clinical features of this type of thyroiditis, and agreement seems universal on these points: the disease is of rather acute onset, often heralded by pain in the throat and frequently associated with fever and malaise and by pain and tenderness in the thyroid gland. The course is usually limited from a few days to a few months. During this period the areas of tenderness and pain often migrate in the thyroid. Thyroid function is normal prior to the onset of the disease. The disease affects females more frequently than males and usually occurs in the fourth or fifth decades.

It is generally agreed that this type of thyroiditis is distinct from and unrelated to Hashimoto and Riedel thyroiditis. The former usually displays a bulky, rubbery, nontender gland and the latter an exceedingly hard, invasively adherent goiter which produces pronounced pressure effects.

Our observations concern 25 patients who had thyroidectomy and 12 who received medical treatment only.

Operative group: 25 cases. This group consisted of 4 males and 21 females. Their ages ranged from 23 to 71 years. The majority of patients (75 per cent) were in the fourth or fifth decades. In 5 patients fever preceded the onset of acute tenderness in the thyroid gland. Careful questioning of patients revealed that the initial pain was "inside the throat" and was not due to tenderness of the thyroid gland itself. Fever was present in 6 patients during observation in the hospital. It was usually constant, ranging from 38 to 39 degrees C., and lasted approximately 1 week in 5 cases but for a period of 3 weeks in 1 instance.

In all patients the initial pain and tenderness developed rather suddenly in one portion of the thyroid gland; in 4 of the patients the pain radiated to the mandibular angle or the ear of the involved side. Dysphagia was pronounced during the early stage of the disease. The constant tenderness usually lasted no longer than 3 weeks. Migration of the sites of pain and tenderness was common. As the tenderness disappeared, the affected portion of the gland became more firm. In 4 patients the tenderness recurred from 3 months to a year after the onset of the acute stage of the disease.

After a period of 2 months symptoms of local pressure consisting of mild dysphagia, choking, and hoarseness dominated the clinical picture. Various medical measures, which will be discussed presently, failed to alter the course of the disease to any appreciable extent.

Thyroidectomy was performed subsequently at periods ranging from 3 weeks to 1 year following the onset of the thyroiditis. However, 80 per cent of the patients had thyroidectomy within 3 months of the onset of

the disease. The indications for operation in the earlier stages of the disease included persistent pain in the thyroid, the belief that hemorrhage into an adenoma had occurred, that hyperthyroidism was present, or because a neoplasm was present. In the later stages operation was performed because of persistent symptoms due to pressure, or because carcinoma was believed to be present. In 3 of the 5 cases in which a preoperative diagnosis of carcinoma was strongly considered, operative findings appeared to confirm the diagnosis. A diagnosis of thyroiditis was not made until the microscopic studies were completed. The clinical diagnosis, which was made preoperatively, was correct in 13 of the 25 patients (52 per cent).

Ten of 13 patients followed from 4 months to 15 years after thyroidectomy became hypothyroid and required therapy with desiccated thyroid. The remaining 12 patients could not be followed. There were no known recurrences of thyroiditis.

Nonoperative group: 12 cases. The sex ratio, age incidence, and symptoms were similar to those of the patients in the group operated upon. A mild pharyngitis or upper respiratory infection associated with weakness and malaise occurred in 3 patients immediately before the onset of recognizable thyroiditis. The majority of patients were observed during the first few weeks of illness. In nearly half the patients the areas of thyroid tenderness migrated within the gland's substance and, in a like number, pain radiated to one or both ears. In 7 patients fever, which usually fluctuated between 38 and 39.5 degrees C., was present during the initial phases of the thyroiditis. Most patients were afebrile within 5 to 12 days, but 1 had fever for over 3 weeks. One patient promptly became afebrile while receiving cortisone, but fever immediately recurred when the drug was discontinued a week later.

Five of the 12 patients were completely free of pain and tenderness in the thyroid gland within 4 weeks after the onset of the disease. In the other 7 patients, 2 to 3 months were required for full recovery. One patient had recurrence of pain and tenderness 4 months following an initial recovery but remained well for the ensuing 2 years. After 3 months, none of the patients had symptoms of pressure although small nodules were palpable in the glands of 2 patients. The glands of 10 patients became essentially normal although slightly firm. Three patients required desiccated thyroid permanently for hypothyroidism following the acute illness. Of the 12 patients in this group, 7 who were followed remained well for periods ranging from 6 months to 7 years.

LABORATORY OBSERVATIONS

Recent clinical reports indicate that the most consistent abnormality during the acute phase of granulomatous thyroiditis is a pronounced elevation of the sedimentation rate. Leucocytosis is observed infrequently. When present, it is not related to the clinical severity of the disease. As stated by Crile and Rumsey (5), the basal metabolic rate is usually within normal limits, although this test is difficult to perform and interpret because of the painful febrile illness.

The serum protein-bound iodine is frequently elevated during the acute phase, but as the process resolves normal values are found. Elevated levels were found in 7 of 8 of our cases in which the serum protein-bound iodine was determined. In 6 patients, the value ranged from 9.7 to 11.6 micrograms per cent, but in 1 severely ill patient the value was 26.0 micrograms per cent, a level which is seldom observed even in severe hyperthyroidism.

Uptake of I^{131} by the thyroid gland is depressed in this disease; in 8 of 9 cases reported by Robbins and co-workers the uptake at 48 hours was only 2.3 per cent or less. Hamilton and his co-workers and Werner and his associates (27) have made similar observations. McConahey and Keating reported that in 11 of 13 patients with acute thyroiditis, uptake of I^{131} at 24 hours ranged between zero and 5.2 per cent; in the other 2 patients the uptake was 10.6 and 18.3 per cent. Crile and Rumsey demonstrated grossly depressed uptakes in 5 of 8 consecutive cases, and made the important observation that this depression occurred even when only one thyroid lobe was involved clinically. In 1 of our patients who received a tracer dose of I^{131} during the acute phase of

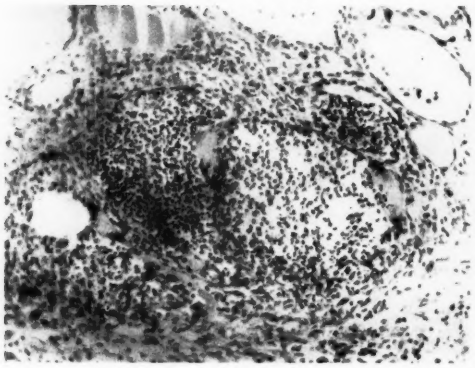

Fig. 1. Early lesion with loss of follicular epithelium and filling of follicular space with neutrophilic leucocytes. Note the perifollicular inflammatory reaction and the adjacent normal follicles. Hematoxylin and eosin, ×60.

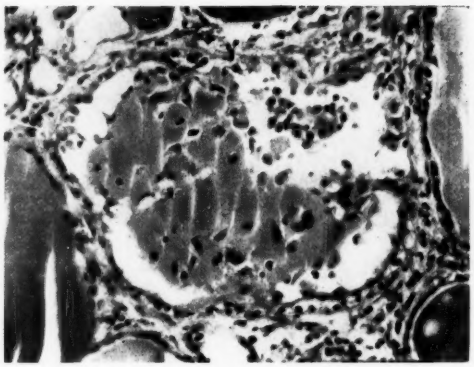

Fig. 2. Early focal lesion with minimal inflammatory reaction. Note fragmenting colloid which has been invaded by inflammatory cells and fibroblasts. Hematoxylin and eosin, ×240.

thyroiditis, the uptake at 5 hours was less than 2.0 per cent.

Robbins and associates reported normal or slightly elevated uptake of I^{131} in 3 patients tested between 4½ and 10 months after the onset of the illness.

The only laboratory tests of value in the diagnosis of granulomatous thyroiditis are the determinations of serum protein-bound iodine and the uptake by the thyroid gland of I^{131}. The protein-bound iodine may be elevated, while the uptake of I^{131} is depressed. In no other thyroid disease does this paradox exist. It seems likely that elevation of protein-bound iodine is the result of follicular destruction associated with absorption of colloid into the blood.

Any theory explaining the depressed uptake of I^{131} in this form of thyroiditis must be based upon the fact that the entire thyroid gland is not necessarily involved in the inflammatory process. Fraser and Harrison believe that injury of the thyroid epithelium by a virus prevents normal uptake of I^{131} but does not simultaneously cause clinically evident thyroiditis in the entire gland. These authors believe that thiouracil prevents or blocks this viral action and thus interrupts the course of the disease. Crile and Rumsey (5) suggested that an increase in the amount of circulating hormonal iodine could in itself cause depression of uptake of I^{131}, since a similar depression results from administration of desiccated thyroid substance. Robbins and his group also suggested that the elevated protein-bound iodine in the serum resulted in suppression of function of the anterior lobe of the pituitary gland. Since depression of uptake of I^{131} may occur even when the level of the protein-bound iodine is not elevated, these authors stated that perhaps the disease itself depressed pituitary function nonspecifically. They further demonstrated that following injection of thyrotropin the uptake of I^{131} rose to normal in 2 of 6 patients. In our series of patients, segments of the thyroid glands not affected by the granulomatous process displayed flattened or inactive follicular epithelium, possibly the result of decreased anterior pituitary activity. This may explain in part the decreased uptake of iodine.

Laboratory diagnosis by needle biopsy in thyroiditis has been advocated by Crile (4). We have not resorted to this procedure because of its potential hazards and because the diagnosis in the earlier stages is usually clinically evident. In the later fibrotic stages, the disease may be confused clinically with other thyroid disorders, including neoplasms. Under these circumstances, surgical exploration and biopsy would seem preferable since a biopsy obtained with a needle may not disclose pathologic and possibly dangerously malignant tissue.

Fig. 3. Later lesion showing more pronounced infiltration of the follicular space by mononuclear cells and partial disappearance of colloid. Note the two peripheral giant cells. Hematoxylin and eosin, ×120.

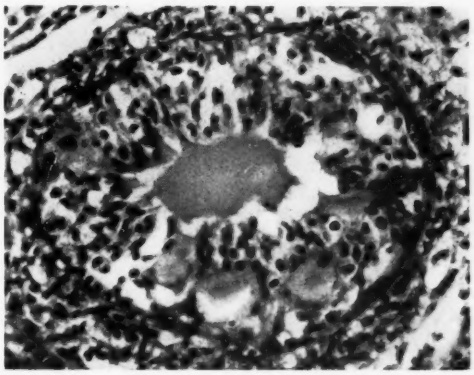

Fig. 4. Similar lesion with replacement of colloid mainly by mononuclear cells and fibroblasts. A few early syncytial groups of cells are observed. Hematoxylin and eosin, ×240.

PATHOLOGIC STUDIES

Gross Examination

The glands were rarely significantly enlarged. The mean weight of the excised tissue was 22.7 grams with a range of 8.5 to 74 grams. Only 10 surgical specimens weighed 25 grams or more. All but 5 of the glands were symmetrical. The majority (22 of 25) were extremely adherent to adjacent structures including the trachea and cervical muscles. The muscles and adhering connective tissues were often edematous; in these instances the thyroid capsule could not be distinguished from the surrounding tissues. One hard fibrous gland caused severe tracheal constriction. The majority of glands had smooth surfaces; nodular bosselations were observed in a few instances, but no discrete superficial nodules were observed. Occasionally the glandular capsules were thickened.

Most glands showed fairly uniform alteration in all portions of the excised tissue. There were varying degrees of fibrous replacement of thyroid parenchyma. Many displayed delicate or coarse fibrous trabeculations interlacing in a red vascular parenchyma, though in some glands the nonfibrotic portions appeared granular and yellowish-gray or pink. In other glands, circumscribed or poorly defined fibrous areas of various size had replaced segments of the two lobes or isthmus. The connective tissue was often resilient or rubbery, but more often was hard and gritty, and was even described as woody or stony in consistency. It was yellow, gray, or white and appeared avascular and ischemic. With greater degrees of fibrosis, there was a corresponding decrease in amounts of visible colloid. In severely fibrosed glands, small irregular islands of residual colloid-containing tissue were observed and displayed the only visible colloid. These areas were sometimes depressed below the cut surface of the thyroid gland. Some of these segments of parenchyma were circumscribed and appeared as small, colloid-containing nodules, generally measuring less than 1.0 centimeter in diameter. Seven of the 25 glands contained one or more of these small discrete nodules, usually lying deeply in the parenchyma. One small nodule was calcified. In one gland small cylindrical plugs of soft yellow tissue were observed throughout an extensively fibrosed parenchyma.

Microscopic Examination

Early lesions. In most instances the earliest lesions are characterized by loss of the epithelium of single follicles within widely scattered lobules. Occasionally two adjacent follicles involved in the process may coalesce, forming one larger diseased follicular space (Fig. 1). Most often, the disappearance of the epithelium is accompanied by localized

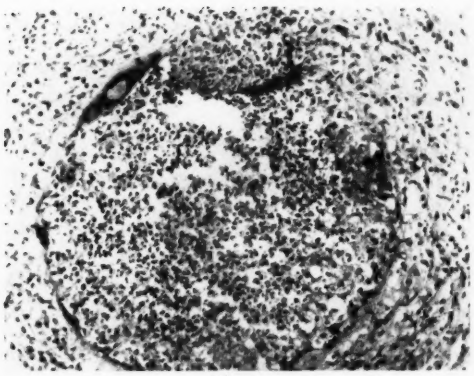

Fig. 5.

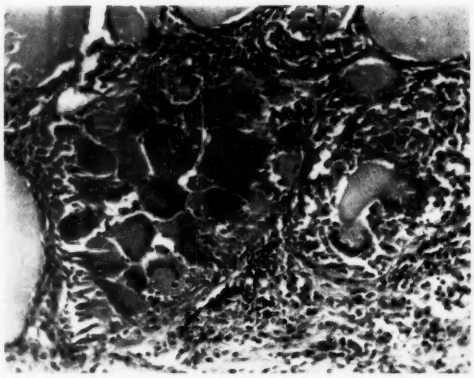

Fig. 7.

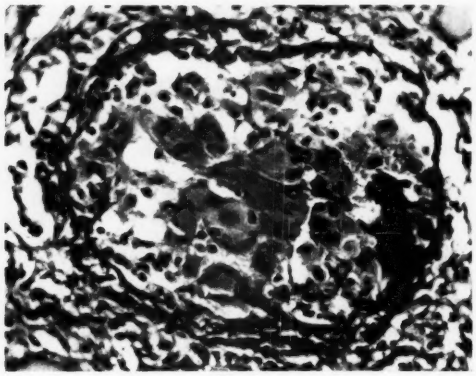

Fig. 6.

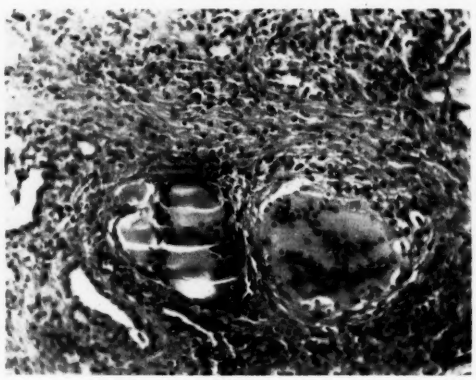

Fig. 8.

Fig. 5. Thyroid follicle distended with purulent exudate. At this stage, several multinucleated giant cells have appeared at the periphery of the follicle at the site of the degenerated epithelium. Note the perifollicular inflammatory reaction and early fibrosis. Hematoxylin and eosin, ×60.

Fig. 6. Thyroid follicle containing small multinucleated cells with abundant, finely granular cytoplasm. Some of these cells closely resemble epithelial elements. Hematoxylin and eosin, ×240.

Fig. 7. Two thyroid follicles which are almost filled with multinucleated cells. Note several normal follicles peripherally. Hematoxylin and eosin, ×120.

Fig. 8. Late lesion with residual giant cells. Two follicles filled with multinucleated cells are seen. Cell on right has about 100 nuclei. Hematoxylin and eosin, ×120.

infiltration of the epithelial layer by many neutrophilic leucocytes, although usually the adjacent colloid and the perifollicular space are also involved (Fig. 1). Occasionally thyroid epithelial cells in various stages of degeneration and necrosis may be observed. As the disease develops the mononuclear cells gradually replace the neutrophilic leucocytes although the latter may persist and be seen in the later, more chronic fibrous lesions. The focal nature of the early inflammatory reaction is characteristic of this disease. Acute epithelial necrosis followed by leucocytic infiltration may occur in a cyclic fashion involving follicles which have been spared in previous acute reactions in adjacent follicles. In addition to the minute focal lesions, one gland in this study displayed necrosis of an entire lobule surrounded by palisading epithelial cells. Although a lobule may be extensively involved in the inflammatory and proliferative process, generally a few follicles are entirely spared even though complete involvement of the thyroid gland may eventually occur.

The colloid within the involved follicles gradually disappears. It often appears frag-

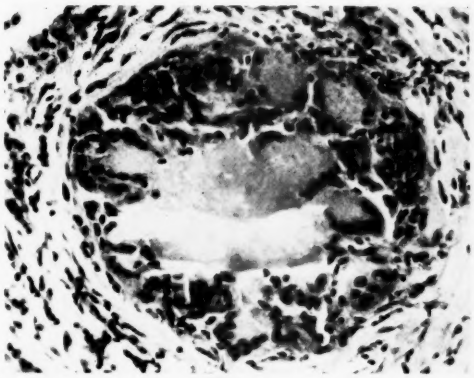

Fig. 9.

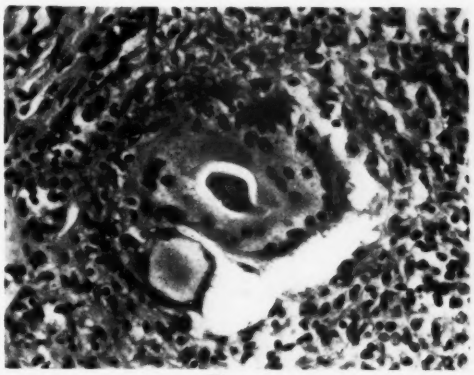

Fig. 11.

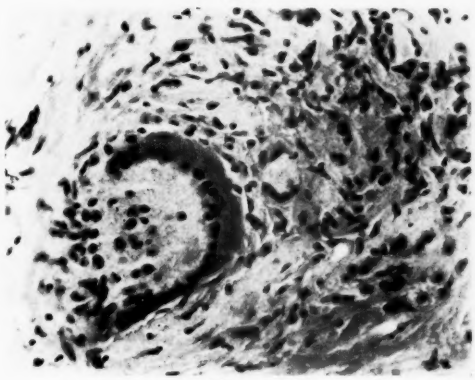

Fig. 10.

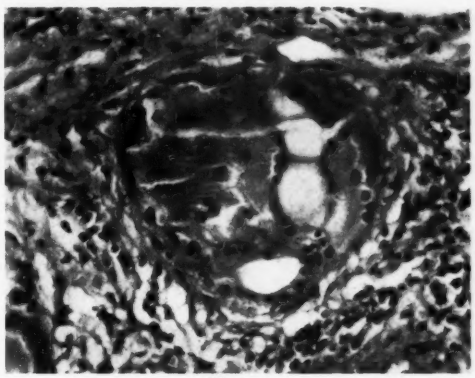

Fig. 12.

Fig. 9. Thyroid follicle displaying numerous giant cells. With the periodic-Schiff stain the junction of the cytoplasm of the giant cells and the colloid is more distinct. Hematoxylin and eosin, ×240.

Fig. 10. Single multinucleated giant cell demonstrating cytoplasmic condensation near the nuclei. Hematoxylin and eosin, ×240.

Fig. 11. Thyroid follicle containing two multinucleated cells, the largest of which contains a colloid fragment inclusion. Note the presence of beginning rarefaction of the cytoplasm of the smaller giant cell. Hematoxylin and eosin, ×240.

Fig. 12. Thyroid follicle containing several multinucleated cells. Note the different degrees of central rarefaction of several of these cells. The lower one displays a central space and thus resembles a follicle. The cells about the space closely resemble epithelium. Hematoxylin and eosin, ×240.

mented and closely resembles fragmenting amyloid substance that is undergoing absorption (Fig. 2). While the neutrophilic leucocytic reaction is still present, the various cellular elements from the remaining follicular wall proliferate and gradually extend into the follicular lumen (Fig. 3). Many of these are large mononuclear cells with the nuclear characteristics of histiocytes or macrophages. The nuclei are oval, indented, or folded, have a delicate chromatin network, and often display one or more small eosinophilic nucleoli. The cytoplasm of these cells may be finely vacuolated or homogeneous and eosinophilic. Accompanying these cells are invading fibroblasts which deposit reticulum and collagenous fibers within the follicular spaces (Fig. 4). This intrafollicular reaction is accompanied by reduplication and thickening of the follicular basement membrane and by variable degrees of perifollicular fibrosis.

Multinucleated giant cells. The characteristic cell observed in most follicles is a multinucleated giant cell which usually appears first in

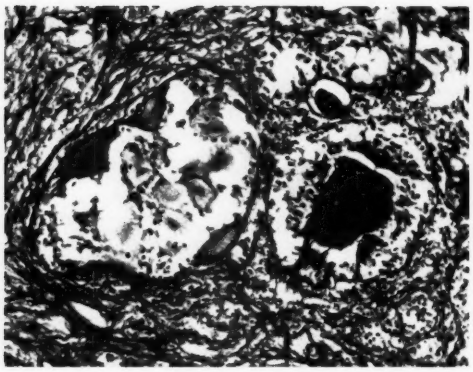

Fig. 13. Several thyroid follicles containing only multinucleated giant cells and fewer mononuclear cells. There is absence of intrafollicular reticulum fibers, although these argentaffin fibrils are numerous in the surrounding tissue. Laidlaw connective tissue stain, ×120.

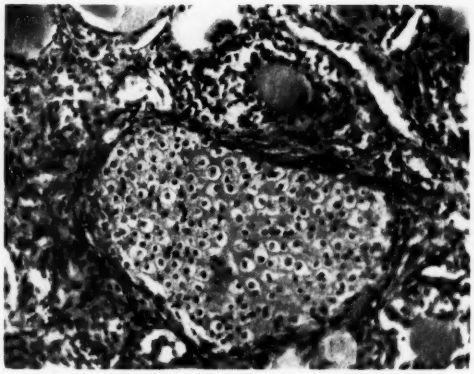

Fig. 15. Thyroid follicle containing only mononuclear cells (histiocytes) which have finely granular cytoplasm. The intercellular substance is homogeneous and eosinophilic and is probably residual colloid. Hematoxylin and eosin, ×120.

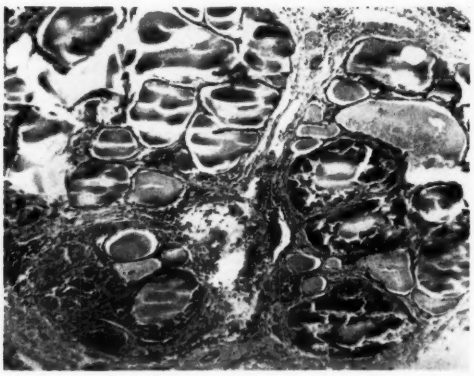

Fig. 14. Early focal giant cell reaction in a few follicles of three adjacent lobules. Notice the minimal perifollicular and interlobular inflammation and scarring. Hematoxylin and eosin, ×60.

those follicles in which neutrophilic leucocytes are still numerous. Here, the multinucleated cells are few and lie adjacent to the remaining follicular basement membrane (Fig. 5). In follicles in which the initial acute inflammatory reaction is minimal or absent, groups of mononuclear or smaller multinucleated cells containing 4 to 6 nuclei may form a flattened cellular layer which replaces the cuboidal epithelial lining, or the small multinucleated cells may be generally distributed in the follicular space (Fig. 6). In some instances this multinucleated cellular layer is separated from the residual colloid by another layer of larger multinucleated cells, obviously of the foreign body type. The smaller peripheral multinucleated cells probably are of epithelial origin and, indeed, continuity of the residual cuboidal follicular epithelium with the peripheral multinucleated cells is occasionally observed. The identical nuclear and cytoplasmic structure (single eosinophilic nucleolus and delicate dispersion of chromatin) of the follicular epithelium and of the peripherally situated multinucleated cells further suggests the epithelial character of these syncytial cells. The early peripheral giant cells may rarely contain mitoses; occasionally they contain a few neutrophilic leucocytes within their cytoplasm.

Generally, those follicles in which multinucleated cells are large and numerous are devoid of colloid, and the follicular space is completely occupied by giant cells. As many as 20 multinucleated cells may distend a follicle (Fig. 7) or a follicle of normal size may be filled with 1 or 2 multinucleated cells of giant size (Fig. 8). Most often the nuclear arrangement of these cells is similar to that of Langhans' giant cells. The nuclei usually number 10 to 20, are peripheral, and assume a horseshoe arrangement, with the open end generally pointing toward the center of the

follicle (Fig. 9). The nuclei are oval or round, contain dispersed chromatin particles, and usually display one or two distinct eosinophilic nucleoli, although occasionally the nucleoli are smaller, multiple, and basophilic. The largest giant cells contain 50 to 100 small, compact, hyperchromatic nuclei which generally lie irregularly in the central portion of the cell. Nucleoli are absent or indistinct.

The cytoplasm of the giant cells varies in appearance. In the Langhans' type of cell, the cytoplasm near the nuclei is eosinophilic, compact, and homogeneous (Fig. 10), whereas that near the residual colloid is finely granular or vacuolated and has a broad zone of adherence to the colloid, although demarcation between the two is distinct. In some instances the remaining central colloid seems to prevent further intrafollicular proliferation of the multinucleated cells which appear flattened and distorted. Occasionally small masses or fragments of refractile eosinophilic substance, presumably colloid, are observed within the cytoplasm of these cells (Fig. 11). Giant cells with centrally placed, smaller nuclei usually have condensed, more deeply eosinophilic nonvacuolated cytoplasm. A variety of histologic stains reveal further cytoplasmic characteristics. The periodic acid-Schiff technique shows fine, uniform, Schiff-positive granules filling the cytoplasm, although there are fewer in that portion adjacent to the follicular colloid. Similar granules are also observed in the cytoplasm of both the intrafollicular histiocytes and the follicular epithelial cells. The colloid stains intensively positive with the periodic-Schiff stain. The cytoplasmic granules appear light or dark pink when stained with the Mallory stain, gray, brown, or black with the Laidlaw stain, and pale green or blue with the colloidal-iron stain. By all methods the colloid stains homogeneously and without granularity.

Eventually, the multinucleated giant cells disappear concomitantly with the appearance of regenerating intrafollicular epithelium. The peripheral arrangement of the nuclei of the giant cell may be associated with extreme central rarefaction and vacuolization and perinuclear condensation of the cytoplasm, producing a follicular structure which, if not a true thyroid epithelial follicle, is a reasonable facsimile (Fig. 12). Since distinct small thyroid follicles which have formed within the original follicular space are seen somewhat later in the process, it cannot be disproved that some giant cells are of epithelial origin. It seems most likely, however, that many of the multinucleated giant cells are of the foreign body variety. In the later stages of the process residual giant cells embedded in extensively scarred lobules may be observed (Fig. 10). When follicles contain only giant

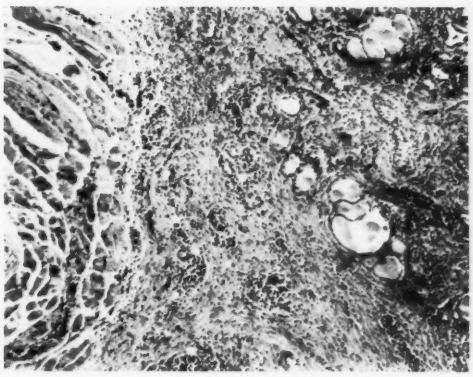

Fig. 16. Periphery of fibrotic gland demonstrating chronic inflammation and fibrosis of the glandular capsule. Note extension of the process into the adjacent striated muscle. Hematoxylin and eosin, ×60 .

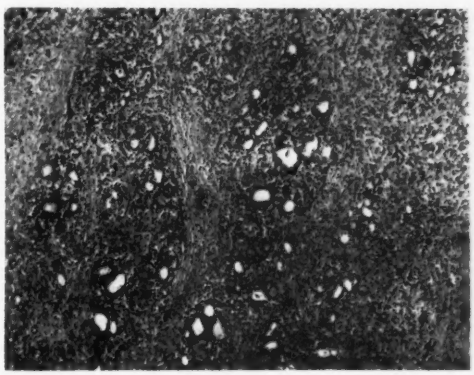

Fig. 17. Late stage showing small reorganized thyroid follicles. Note that the small lobules correspond to the previous follicles which are now filled with the reorganized epithelium. There is both intralobular and interlobular fibrosis, and the residual inflammatory infiltration is diffuse. Hematoxylin and eosin, ×60.

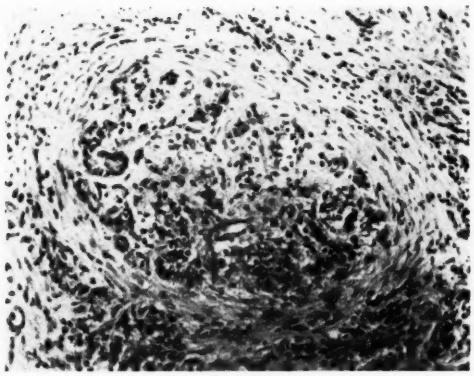

Fig. 18.

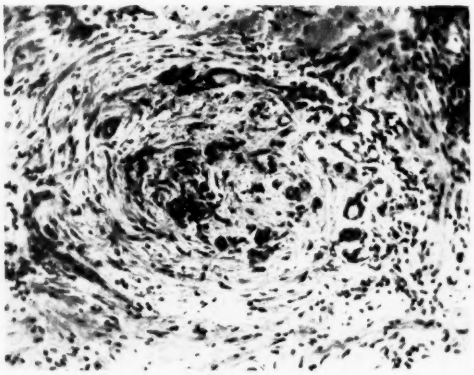

Fig. 20.

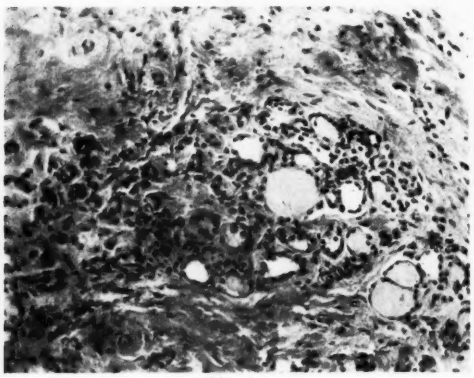

Fig. 19.

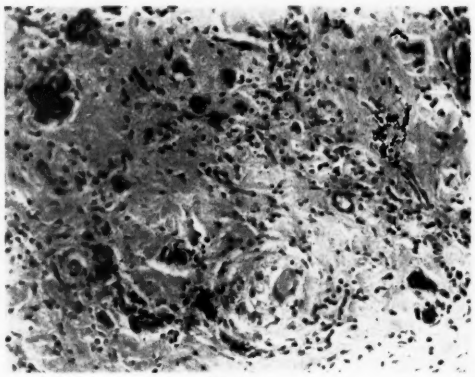

Fig. 21.

Fig. 18. Thyroid follicle which is now filled with regenerated epithelium some of which has formed small follicles which are supported by connective tissue. The outline of the original follicle is still visible although it is accentuated by fibrosis. Hematoxylin and eosin, ×120.

Fig. 19. Further differentiation of the small thyroid follicles. Several have accumulated colloid. Note the fibrillary character of the surrounding fibrous tissue. Hematoxylin and eosin, ×120.

Fig. 20. Altered thyroid follicle in which fibrous proliferation has exceeded epithelial regeneration (as in Figs. 18 and 19). The few small follicles observed are compressed and distorted. Hematoxylin and eosin, ×120.

Fig. 21. Late stage demonstrating extensive fibrosis with minimal epithelial regeneration. The outlines of the previously existing follicles are almost obscure. Note the single degenerating giant cell below. Hematoxylin and eosin, ×120.

cells and histiocytes, reticulum fibers within the follicles cannot be demonstrated (Fig. 13), whereas when intrafollicular fibroblasts appear, reticulum fibers likewise are seen.

In a few glands it is apparent that the initial injury to the thyroid epithelium has been less severe, since disappearance of the epithelium may not be accompanied by neutrophilic leucocytic infiltration. Such lesions are characterized solely by proliferation of syncytial giant cells. The basement membrane of the involved follicle remains intact, and there is no peripheral inflammatory reaction. In these glands the focal nature of the process is also evident (Fig. 14). In some instances only a small segment of an affected follicle shows a proliferative syncytial, inflammatory, and epithelial regenerative reaction.

Some affected follicles are devoid of giant cells. In these, numerous mononuclear cells of the macrophage type fill the follicular spaces and are surrounded by protein-containing fluid which may be fluid colloid (Fig. 15). Other follicles filled with histiocytes closely

resemble tubercles. Still others retain their original size and outline though their lumens contain no colloid and few cells. Nonprotein-containing fluid, then, must largely occupy these follicular spaces.

Inflammatory reaction. Generally, the inflammatory and proliferative changes within the follicles are accompanied by considerable perifollicular inflammatory reaction, characterized by infiltration with lymphocytes and often by numerous eosinophilic leucocytes. Plasma cells, occasionally binucleated, are present in moderate numbers. Histiocytes with oval, round, or elongated and indented nuclei and vacuolated cytoplasm, identical with some intrafollicular cells, also infiltrate the perifollicular connective tissues. In some instances, mast cells are also observed in the inflammatory reaction. The early inflammatory connective tissue has an extremely edematous and basophilic mucoid character, and appropriate stains show an abundance of acid mucopolysaccharides. Fibroblastic proliferation is accompanied by the appearance of numerous small capillaries. As the lesion becomes older the mucoid appearance of the intercellular substance is lost, and moderately dense, but persistently fibrillary collagen replaces the mucopolysaccharides. In the later stages fibrous replacement of the thyroid parenchyma may be considerable; not infrequently it involves the capsules and the perithyroidal tissues, which explains the adherence of the gland to surrounding structures (Fig. 16).

The thyroid nerves appear prominently in the fibrous tissue; these structures, however, are neither fibrotic nor infiltrated with inflammatory cells. In some glands intrafollicular alteration with an abundance of multinucleated cells or even reasonably complete epithelial regeneration is accompanied by little or no perifollicular fibrosis or inflammation.

Generally, the inflammatory reaction in the later fibrosed and partially regenerated glands is less severe, diffuse, and mainly lymphoid (Fig. 17). Only rarely are discrete lymphoid follicles with germinal centers observed; these are rather closely associated with regenerating epithelium.

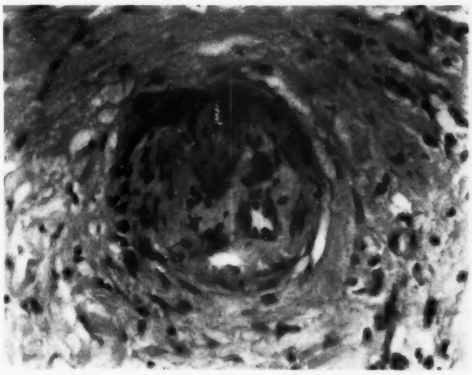

Fig. 22. Small artery in late stage of thyroiditis. Both intimal fibrosis and medial hyperplasia have resulted in pronounced narrowing of the lumen. Hematoxylin and eosin, ×240.

Thyroid epithelial regeneration. Characteristically, the originally injured follicle regenerates in a peculiar fashion. Groups of epithelial cells arise from residual epithelium lining the follicles, perhaps through the medium of syncytial giant cells, and invade the follicular space together with the mesodermal cells. Eventually the epithelium forms follicular structures which are supported by fibroblastic cells. The latter produce a mucoid and collagenous stroma (Fig. 18). The newly developed follicles, at first extremely small, increase in size and eventually contain pale colloid (Fig. 19). The enlargement of the new follicles occurs at the expense of the supporting mucoid stroma, the process closely resembling the acinar growth in a lobule of the breast at the expense of the mucoid periductal fibrous tissue. The epithelial cells of a few newly formed follicles contain golden-brown pigment granules.

The proliferation of fibrous tissue within and about the newly formed follicles may be so excessive at times that thyroid epithelial regeneration is minimal (Fig. 20) or fails. In these instances, the original follicle becomes obliterated by fibrous tissue, and its borders disappear into the fibrosing lobule (Fig. 21). Abundant scarring may isolate one or two residual giant cells in an otherwise obliterated follicle. Some follicles are compressed and elongated by proliferating connective tissue.

Secondary hyperplasia. In the late extensively fibrous lesions, the remaining uninvolved parenchyma generally shows a significant degree of hyperplasia, probably compensatory in nature, which is characterized by heightening of the follicular epithelium and pallor and peripheral vacuolization of the colloid. In this disease, nodular hyperplasia does not occur. In the less extensively diseased glands, in the earlier stages of the disease, the uninvolved follicular epithelium is flattened.

Vascular lesions. A variety of vascular lesions, probably secondary to the interstitial inflammatory reaction, are observed in this disease in the later stages only. All the layers of some of the large and medium-sized veins are infiltrated with lymphocytes. Some venous lumens are almost completely obliterated by delicate connective tissue containing infiltrating lymphocytes and small capillary vascular channels. These venous lesions appear most prominently in heavily scarred areas where little or no epithelial regeneration has occurred. Likewise, in the unusually fibrotic glands, the medium-sized arteries occasionally have thickened intimal layers composed of mucoid connective tissue. Smaller arteries occasionally display pronounced intimal hyperplasia, with extreme narrowing of their lumens (Fig. 22). Larger arteries often have deposits of mucoid substance in their medial layers, at times associated with focal calcification of the media or of the fragmented internal elastic membrane. These lesions of the larger arteries in no way differ from those commonly found in thyroid glands of older persons.

Miscellaneous. A few of the epithelial cells in the small reorganized follicles show the changes presumed to be those of "exhaustion," characterized by pleomorphic, homogeneous and hyperchromatic nuclei and an abundance of eosinophilic cytoplasm.

Histologic examination of these glands with the Giemsa and Macchiavello stains shows no nuclear or cytoplasmic inclusion bodies either in the involved or normal-appearing portions of the glands.

The extent and degree (acute and chronic) of the inflammatory reaction and epithelial reorganization showed no correlation with the clinical duration or course of the disease.

Radioautographic Studies

A radioautograph was made in 1 case (2½ months' duration). The normal-appearing follicles of uninvolved lobules showed considerable diffuse uptake of I^{131}, although the uptake appeared less than normal. In follicles which displayed early peripheral proliferative reactions but still retained colloid, the uptake was slightly less. There was no uptake in follicles filled with mononuclear or giant cells. In lobules in which both damaged and normal follicles were present, minimal or no uptake was observed in the normal-appearing follicles. Most of the smaller regenerated and reorganized follicles showed no uptake but, in some of the slightly larger reorganized follicles containing colloid, moderate uptake in the follicular spaces was observed.

Comment

The histologic characteristics of granulomatous or giant-cell thyroiditis are similar superficially though actually distinctly different from those of chronic thyroiditis of the Hashimoto type. In both instances, intrafollicular proliferation of residual epithelium follows the original insult to the follicular lining. This proliferation results in the formation of small follicles which eventually contain colloid. In granulomatous thyroiditis these newly formed follicles appear to remain small but presumably function. The regenerated follicles in Hashimoto thyroiditis may continue to enlarge and approach the size of normal follicles.

Numerous intrafollicular giant cells which are characteristic of the lesions of granulomatous thyroiditis occur much less frequently in Hashimoto thyroiditis (16). The origin, function, and fate of these multinucleated cells are of considerable interest. Goetsch studied these cells in glands classified as Riedel thyroiditis but which showed the typical lesions of granulomatous thyroiditis. His review of the literature indicated wide differences in opinion regarding the origin and function of these cells, although the majority of investigators believed them to be

of epithelial origin. De Quervain in his classical descriptions (9, 10) of this disease could not dismiss the epithelial origin of these cells. Goetsch concluded that (1) the giant cells were formed by fusion of desquamated epithelial cells, since the colloid disappeared without evidence of phagocytic activity of the multinucleated cells, and (2) these epithelial giant cells finally disappeared.

Our studies suggest that some of the multinucleated giant cells are probably of epithelial origin and, indeed, may later become small thyroid follicles. Other multinucleated cells, however, have a structure identical with that of foreign body giant cells, including the Langhans' cell of tuberculous lesions.

In both granulomatous and Hashimoto thyroiditis the intrafollicular epithelial growth is accompanied by intrafollicular invasion of supporting connective tissue. More often in granulomatous thyroiditis complete fibrous obliteration of the original follicular space may occur.

In granulomatous thyroiditis the intrafollicular and perifollicular connective tissue is distinctly mucoid in character but becomes more collagenous as the disease progresses. Even in extensively fibrosed glands, this connective tissue retains a fibrillary character. In contrast, the fibrous tissue in Hashimoto thyroiditis appears as broad branching bands of compact and hyalinized collagen. In both types of thyroiditis, fibrosis of the capsule, with fibrous and inflammatory extension to the perithyroid tissue, occurs, thus accounting for adherence to the surrounding tissues often observed. The invasive quality of the fibrous tissue characteristic of Riedel thyroiditis, however, is not seen in granulomatous or Hashimoto thyroiditis (16).

The inflammatory reaction in granulomatous thyroiditis usually consists first of an infiltration of neutrophilic leucocytes in and around the degenerating follicles. In time there is replacement by a variety of inflammatory cells, including lymphocytes, macrophages, plasma cells, eosinophilic leucocytes and fewer mast cells. In general, the infiltration is not pronounced and tends to be diffuse, although earlier the reaction occurs mainly about involved follicles and lobules. The appearance of lymphoid follicles with germinal centers is unusual. In Hashimoto thyroiditis an abundance of lymphoid tissue, focally distributed and associated with the presence of lymphoid follicles, is commonly observed; some glands contain numerous plasma cells as well. The infiltration of these cells in Hashimoto disease is probably not a true inflammatory reaction.

In granulomatous thyroiditis the regenerated epithelium only rarely shows the cellular changes associated with "exhaustion", i.e., nuclear hyperchromatism and pleomorphism and cytoplasmic eosinophilia. Thus, most glands contain sufficient unaffected glandular tissue so that the newly regenerated thyroid epithelium is not subjected to excessive stimulation. In contrast, the gland of Hashimoto thyroiditis characteristically displays the cellular changes of exhaustion at any stage of the process; the regenerated epithelium likewise is often so altered.

In thyroid glands in which there is extensive involvement by the granulomatous process, the unaffected follicular epithelium in a few instances may be moderately hyperplastic. This is undoubtedly compensatory. In Hashimoto thyroiditis compensatory hyperplasia, when present, generally affects the regenerated follicles.

Although true hyperthyroidism does not occur in granulomatous thyroiditis, the protein-bound iodine of the serum may be elevated in some instances. This increase is readily explained by excessive absorption of colloid from follicles which have lost most of their epithelial lining. When hyperthyroidism is observed in Hashimoto thyroiditis, it appears to result from the thyroid hyperplasia which antedates and is probably one of the initial lesions of Hashimoto thyroiditis.

A significant relationship has been shown to exist between Hashimoto thyroiditis and malignant thyroid neoplasms (16). In glands affected by granulomatous thyroiditis, neoplasms (benign or malignant) have not been observed.

The general tendency is to classify as Riedel thyroiditis those glands which are hard, fibrous, or woody and adherent to the surrounding tissues. This classification has led to some

confusion since one terminal stage of several inflammatory processes may display a hard, adherent thyroid gland. The term Riedel thyroiditis has been reserved for those glands containing degenerated involutionary nodules surrounded by proliferating fibrous tissue which characteristically locally invades the adjacent cervical structures. Extensive fibrosis may occur in Hashimoto thyroiditis and, while there may be some degree of adherence to surrounding tissues, the capsular connective tissue lacks the aggressive invasive qualities seen in Riedel thyroiditis. In granulomatous thyroiditis fibrosis of the entire gland may result from extensive disease. Such a hard gland, often adherent to the trachea and cervical muscles, may cause tracheal compression. The classic descriptions of Riedel (20–22), although incomplete, have delayed appreciation of the fact that at least three distinct thyroid diseases may produce extensive thyroid fibrosis and glandular adherence.

THERAPY

Hot compresses or ice collars together with aspirin, codeine, and a soft diet are appropriate general measures.

Spontaneous remissions and exacerbations characteristic of the disease make evaluation of therapy extremely difficult. There are no convincing reports that any of the antibiotics alter the course of granulomatous thyroiditis.

King and Rosellini reported that thiouracil caused a remission of the disease in their 8 patients. Fraser and Harrison obtained improvement in 3 patients within 2 days with methylthiouracil, and remission was complete within 2 to 4 weeks. Reveno and Rosenbaum reported relief of acute thyroiditis in 3 patients, 2 of whom received tapazole® (10 to 15 mgm. daily) and 1 of whom received thiouracil (300 mgm. daily). Nine to 12 days were required for recovery. These authors stated further that appraisal of the effect of these agents is difficult since their patients were treated in the later stages of the disease when spontaneous resolution may have been underway. Westwater, in discussing 21 cases of acute thyroiditis, expressed the opinion that recovery was hastened in the 4 patients who received propylthiouracil.

Crile and Rumsey (5) described striking symptomatic relief and decrease in the size of the thyroid gland in 14 of 35 patients given x-ray therapy within 1 week of commencing treatment. The total average dose was 800 roentgens (100 to 150 r daily). The remainder of the 35 patients showed less improvement. In 6 cases recurrences developed about 6 weeks later; these were readily controlled with a small additional dose of radiation. Osmond and Portmann described beneficial effects of irradiation in subacute thyroiditis and noted that 40 of their 55 patients were cured after one course of treatment. Allen and Reeves likewise believed that external irradiation (500 to 1500 r) was a distinct aid in shortening the course of the disease and in producing symptomatic relief. Nearly 2 weeks was necessary for full relief; recurrences developed in only 4 of 15 (27 per cent) patients treated with irradiation, whereas 8 of 21 (38 per cent) nonradiated patients had recurrence.

Crile and Schneider (6) noted both subjective and objective improvement in subacute thyroiditis when cortisone or corticotropin were administered. Cortisone, 100 milligrams daily, brought about relief from pain in 4 hours and striking reduction in the size of the thyroid in 48 hours. Corticotropin, 80 units, administered intravenously resulted in relief of thyroid tenderness in 6 hours and decrease in firmness of the gland within 2 hours. Corticotropin or cortisone was given to 6 patients with acute thyroiditis by Werner (26) who emphasized that the patients became afebrile while receiving these drugs and that fever and pain promptly recurred when the agent was discontinued. Clark and his associates likewise obtained prompt beneficial effects in 3 patients given cortisone in a dose of only 25 milligrams daily. Pronounced relief occurred in 24 hours; the patients recovered fully within a week, although the drug was continued for a second. Robbins and coworkers noted definite clinical improvement in 4 of 6 patients who received thyrotropin. Improvement occurred within 2 days, but all relapsed within a week. Why this substance produced improvement is obscure.

Significant responses to antithyroid drugs have not been observed by us. Our expe-

riences substantiate the results of x-ray therapy. Satisfactory temporary results were obtained in 1 patient treated with cortisone after the method of Clark and co-workers. In general, our patients received only symptomatic treatment, and evaluation of specific medical therapy has been limited. However, our series of patients has served to clearly delineate the natural course of the disease.

Use of x-ray or cortisone or both seems the preferable mode of therapy at present, since these agents probably act on the inflammatory process in the thyroid gland as they do elsewhere. We believe, however, that such therapy need not be employed initially, unless symptomatic treatment fails to relieve discomfort within a reasonable period. Although the majority of our patients had thyroidectomy, surgical treatment is seldom required unless medical therapy fails, carcinoma is suspected, or the fibrosed thyroid gland eventually produces symptoms due to thyroid pressure.

SUMMARY AND CONCLUSIONS

1. A series of 37 patients with granulomatous or giant-cell thyroiditis has been reviewed.

2. The clinical diagnosis in the early stages should be made readily; in the later stages the fibrosed gland may simulate other thyroid diseases, including carcinoma.

3. The level of the serum protein-bound iodine may be moderately elevated, and the uptake of I^{131} is severely depressed during the acute phase of this disease.

4. Thyroidectomy is seldom required unless symptoms resulting from thyroid pressure are present or if carcinoma is suspected.

5. This type of thyroiditis is a distinct pathologic entity and is characterized by focal follicular degeneration associated with acute inflammation, followed by proliferation of epithelial and mesodermal cells of the residual follicular wall. Reorganization of small thyroid follicles probably originates in part from multinucleated giant cells. A hard, adherent thyroid gland may result from extensive glandular fibrosis.

6. When symptomatic therapy fails, external radiation of the thyroid gland may hasten resolution of the process, and administration of cortisone may effectively interrupt the course of this thyroid disease. Antibiotics appear to be without value; beneficial effects of thiouracil compounds have not been clearly established.

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THE EFFECTS OF GASTRIC ANACIDITY UPON THE METABOLIC ALTERATIONS INDUCED BY GASTRIC ASPIRATION

IRVING M. ARIEL, M.D., F.A.C.S., New York, New York

METABOLIC alterations induced by the withdrawal of gastric secretions have been extensively investigated. The effects upon the plasma crystalloid changes, the altered fluid distribution, and the tissue electrolyte alterations have been described.

Such studies performed on man have usually lumped the data under a single heading with no attempt to discern if a difference in response is produced by patients with high acidity of their gastric contents (a marked preponderance of chloride over the cation content) and by those with so-called gastric anacidity.

This study investigates those alterations in fluid and electrolyte balance in 5 patients who have a low free acid content of the gastric secretions. The induced electrolyte alterations differ from patients with gastric hyperacidity in that the latter group manifest a marked hypochloremia and alkalosis(2), whereas those with gastric anacidity may suffer a rather profound loss of total body electrolytes with but minor alterations in the serum concentrations of the lost ions. Since patients with gastric cancer usually manifest gastric anacidity, it is pertinent to review the alterations induced by gastric aspiration in these patients and to distinguish the difference in the response of the two groups. This investigation focuses attention upon the alterations in the quantity and distribution of body water, changes in serum and tissue electrolytes, and discusses their clinical significance.

PROCEDURE

Five patients with gastric cancer were depleted of electrolytes by the continuous withdrawal of gastric contents through an indwelling gastric tube attached to gastric suction for from 3 to 6 days. Gastric secretion was stimulated by the oral ingestion of 30 milliliters of 7 per cent ethyl alcohol every 4 hours during waking hours. These patients were chosen because they all presented a very low free acid content of the gastric secretions. Each patient was given intravenously a large amount of fluid, such as 5 per cent dextrose in distilled water. At the completion of the experiment they were given from 13.5 to 27 grams of sodium chloride as normal saline solution intravenously each day until the serum electrolytes were normal.

The following determinations were performed: (1) serum, gastric juice, and urinary electrolytes, (2) alterations produced in total body water, interstitial water, and plasma volume, and (3) changes produced in the water and electrolytes of striated muscle.

CHEMICAL METHODS AND CALCULATIONS

Serum chloride determination was performed by the technique of Schales and Schales. Serum protein concentrations were determined by the method of Weichselbaum, serum, urine, and gastric sodium and potassium by an internally compensated Perkin-Elmer flame photometer, and the hematocrit as described by Musser and Wintrobe. The carbon dioxide combining capacity was determined by the gasometric method of Van Slyke and Cullen(13). Urine chloride concentrations were ascertained by the modified Volhard-Harvey titration method. Plasma volume and thiocyanate (available fluid) space were measured by the procedure developed by Gregersen and Stewart adapted for the Evelyn colorimeter.

Total body water was determined by deuterium dilution and analyzed by the mass spectrograph. The blood sample obtained

From the Pack Medical Group, New York, New York, and the Department of Surgery, University of Minnesota, Minneapolis, Minnesota.

after the administration of 25 grams of deuterium oxide was vacuum distilled to evaporate the water, which was placed in an equilibrium tube with a catalyst (platinum oxide) and was frozen in an alcohol-dry ice bath. The air above the water and catalyst was removed by a vacuum pump and this air was replaced by hydrogen gas after which the equilibrium tube was sealed and allowed to stand overnight. During this period the hydrogen gas and the hydrogen atoms of the water would exchange. After equilibrium had occurred, the hydrogen gas was analyzed by the mass spectrograph for the deuterium content.

METHODS OF CHEMICAL ANALYSIS OF MUSCLE BIOPSIES

Muscle biopsies averaging 2 grams were obtained from either the deltoid or gastrocnemius muscle. The opposite muscle was usually analyzed when several biopsies were taken from the same patient. Anesthesia was obtained by infiltrating the skin and subcutaneous tissue with 1 per cent procaine at a significant distance from the site where the muscle was to be obtained.

The muscle biopsy was quickly blotted with dry gauze. The fresh tissue was freed of visible fat and some connective tissues with a scissors and placed into a tarred weighing bottle. The water content was determined by drying the tissues overnight in an electric oven at 105 degrees C. Fat was determined by extracting the tissue with ethyl ether and petroleum ether, according to the method of Hastings and Eichelberger. The dry tissue was then divided into two parts and the chloride content was determined on 1 aliquot after boiling with concentrated nitric acid in the presence of an excess of silver nitrate, and analyzed by the Volhard titration technique. The sodium and potassium contents were determined by means of an internally compensated flame photometer on the other portion of tissue which was ashed overnight in a platinum crucible in an oven at 450 degrees C.

All values are presented in terms of fat-free weight since fat is deposited dry. Actually all muscle analysis must be presented on the basis of fat-free weight because the addition of this variable produces uncomparable results.

Electrolyte concentration of extracellular fluid as milliequivalents per kilogram of water was calculated by the method described by Yannet and Darrow.

$$\frac{[Cl]_{ser}}{0.95[H_2O]_{ser} \times 0.95} = [Cl]_e$$

$$\frac{[Na]_{ser} \times 0.95}{[H_2O]_{ser}} = [Na]_e$$

$$[K]_e = [K]_{ser}$$

Muscle per 100 grams fat-free solids (FFS)

$$(H_2O)_e \text{ in gm.} = \frac{(Cl-1)}{[Cl]_e}$$

$$(Na)_e \text{ in mM.} = (H_2O)_e \times [Na]_e$$

$$(Na)_i \text{ in mM.} = (Na) - (Na)_e$$

In the equations above, subscripts "ser," "e," and "i" refer to serum, extracellular, and intracellular phases respectively.

[ ] refers to concentration.

( ) refers to total amount expressed in Millimols milliequivalents, or grams.

RESULTS

The data are summarized in Tables I to VIII and can be best presented by describing the component parts of this study separately.

THE QUANTITY AND ELECTROLYTE CONTENT OF THE GASTRIC ASPIRATE

The total quantity of gastric juice aspirated averaged 4.8 liters and fluctuated between 3.5 and 5.5 liters.

The chloride content of the gastric fluid varied from 62 to 96 milliequivalents per liter and averaged 77 milliequivalents per liter. The total quantity of chloride withdrawn in the aspirate fluctuated from 297 to 518 milliequivalents and averaged 369 milliequivalents.

The potassium content was significant and fluctuated between 8 and 17 milliequivalents per liter. The average total quantity of potassium aspirated in the gastric content was 60 milliequivalents.

THE ALTERATION OF SERUM CONCENTRATION OF DIFFERENT CONSTITUTENTS INDUCED BY WITHDRAWING GASTRIC CONTENTS

The alterations of serum concentrations of hemoglobin, protein, urea nitrogen, and electrolytes are presented in Table II. There were minor variations in the hemoglobin concentrations of all the patients, with a tendency toward a slight rise in hemoglobin concentration. The hematocrit increased in each of the

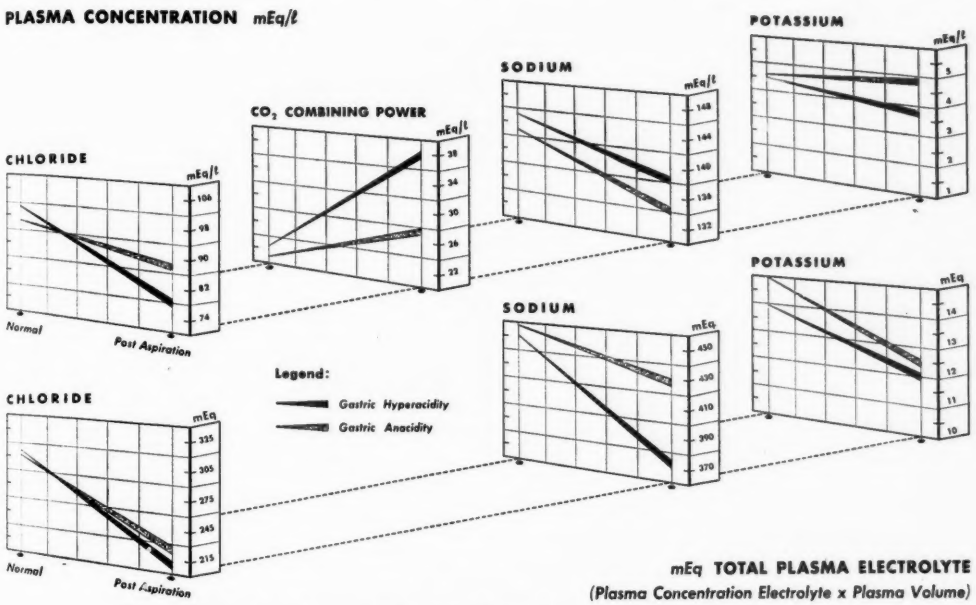

Fig. 1. Effects of gastric composition upon plasma electrolyte content by gastric aspiration.

patients studied, at times to a rather marked degree. This is interpreted as a manifestation of hemoconcentration. There was also an increase in the serum protein concentration and blood urea nitrogen.

The most significant changes occurred in the serum electrolytes. The serum chloride decreased in varying amounts in the different patients. In Case 2, it decreased slightly from 95 to 92 milliequivalents per liter, in Case 3 it diminished 20 milliequivalents per liter. The average decrease was 12 milliequivalents per liter.

A concomitant but rather limited rise of the carbon dioxide combining power occurred. In no instance did a severe alkalosis develop and it is noteworthy that, despite a rather low serum chloride content in several of the patients, a marked increase in carbon dioxide combining power was not observed. The average increase was 7 milliequivalents per liter.

The serum sodium content diminished in each patient, the average decrement being 9 milliequivalents per liter. The potassium concentration of the serum fluctuated. It decreased somewhat in 2 of the patients, and increased in the 3 remaining patients.

THE URINARY EXCRETION OF ELECTROLYTES DURING THE WITHDRAWAL OF GASTRIC JUICE

The data demonstrate that in the presence of electrolyte deficiency water cannot be retained even though needed and is excreted; a dehydration of depletion develops.

The urinary excretion of electrolytes during the first half of the experiment is compared to that during the second half to note if a direction of shift occurs as the withdrawal of gastric juice continues (Table III).

The *chloride content* of the urine remained low throughout. The average urinary chloride of 2 milliequivalents per liter during the first half of the experiment resulted in a total excretion of 12 milliequivalents of chloride. During the second portion of the experiment a further diminution of the chloride concentration to 1.5 milliequivalents per liter resulted in a total excretion of 9 milliequivalents of chloride.

TABLE I.—THE CONTENT OF CHLORIDE, SODIUM, AND POTASSIUM OF THE FLUID WITHDRAWN BY GASTRIC ASPIRATION IN PATIENTS WITH GASTRIC CARCINOMA

Case No. Patient	Quantity of gastric fluid aspirated, liters	No. of days of withdrawal	Chloride		Sodium		Potassium	
			mEq./l.	Total amount aspirated, mEq.	mEq./l.	Total amount aspirated, mEq.	mEq./l.	Total amount aspirated, mEq.
1 L.G.	3.5	6	85	297	80	280	10	35
2 C.V.	5.4	4	96	518	92	487	12	65
3 B.B.	4.5	5	76	342	74	333	15	67
4 J.C.	5.3	5	62	329	59	323	17	90
5 M.L.	5.5	4	65	357	60	330	8	44

The sodium excretory pattern was the same during both portions of the experiment. During the first half, the average concentration of urinary sodium was 2.4 milliequivalents per liter with a total excretion of 13 milliequivalents. During the second portion of the experiment an average sodium concentration of 2.3 milliequivalents per liter resulted in a total excretion of 15 milliequivalents of sodium.

The *potassium* excretion in the urine more or less paralleled the sodium excretory pattern in that there was very little change in the total quantity excreted during both portions of the experiment. During the first days of gastric aspiration an average of 15 milliequivalents of potassium was excreted which ranged from 9 to 23 milliequivalents. During the second half of the experiments an average of 13 milliequivalents of potassium was excreted and the variation in amount was between 8 and 18 milliequivalents.

THE EFFECT OF WITHDRAWING GASTRIC CONTENTS UPON BODY WEIGHT, TOTAL BODY WATER, AND CORPOREAL DISTRIBUTION OF WATER

Weight and total body water alterations (Table IV). There was a rather significant drop in weight, the average decrease being 4.8 kilograms. This decrease in body weight occurred because the patients could not retain water in the presence of a crystalloid deficit. This loss of total body water was measured by the deuterium dilution technique in 2 patients. A decrease of total body water equal to 4.5 and 3.4 liters was demonstrated.

TABLE II.—ALTERATIONS IN SERUM CONCENTRATION OF HEMOGLOBIN, PROTEIN, AND ELECTROLYTES INDUCED BY WITHDRAWING GASTRIC CONTENTS

Case No.		Hemoglobin, gm. per cent	Hematocrit, per cent	Protein, gm. per cent	Blood urea nitrogen, mgm. per cent	Chloride, mEq./l.	CO_2 combining power, mEq./l.	Sodium, mEq./l.	Potassium, mEq./l.
1	Normal	15	46	7.0	10	100	22	146	5.0
	After aspiration	14.6	49	7.6	14	86	27	137	4.8
2	Normal	14.0	42	6.5	9	95	21	150	4.1
	After aspiration	15.5	48	7.2	12	92	24	135	5.2
3	Normal?	15.2	45.5	—	—	84	28	136	4.5
	After aspiration	—	—	6.2	—	64	—	132	4.8
4	Normal	12	38	6.1	8	98	20	145	5.0
	After aspiration	14.5	45	6.8	15	90	32	130	4.5
5	Normal	13	46	6.2	8	96	21	140	4.5
	After aspiration	14.5	47	6.9	12	82	28	137	4.9

TABLE III.—URINARY EXCRETION OF ELECTROLYTES DURING THE WITHDRAWAL OF GASTRIC CONTENTS

Case No.	Averages of experiments	Urine volume	Chloride		Sodium		Potassium	
	No. days	liters	mEq./l.	Total excreted, mEq.	mEq./l.	Total excreted mEq.	mEq./l.	Total excreted, mEq.
1	1st half, 2	5.2	2.2	11.4	3.1	16.1	3.5	18.2
	2nd half, 2	6.5	2.0	13	3.1	20	2.0	13
2	1st half, 3	4.0	3.0	12	3.5	14	2.2	8.8
	2nd half, 3	5.2	2.5	13	1.2	6.2	1.5	7.7
3	1st half, 4	7.5	1.5	11.2	1.8	13.5	2.0	15
	2nd half, 3	7.0	1.0	7.0	1.0	7.0	1.8	12.6
4	1st half, 3	6.5	1.8	11.7	2.0	13.0	3.5	22.7
	2nd half, 3	7.0	1.0	7.0	3.5	24.5	2.6	18.2
5	1st half, 2	6.0	2.0	12.0	1.8	10.8	1.9	11.4
	2nd half, 2	7.5	1.0	7.5	2.5	18.7	1.8	13.5

Plasma and extracellular volume alterations. An average decrease of plasma volume equivalent to 0.6 liter and a decrease in the interstitial space equal to 2.5 liters were observed. Thus an average of 3.1 liters was lost from the extracellular space (serum and interstitial space) and a smaller quantity (1.7 liters) probably lost from the intracellular compartment.

THE ALTERATIONS INDUCED BY WITHDRAWAL OF GASTRIC CONTENT UPON MUSCLE ELECTROLYTES AND WATER

A sample of muscle was analyzed before and after depletion (Tables V and VI). An average loss of water equal to 34 milliliters per kilogram of muscle occurred. The muscle water in all patients diminished. A diminution of chloride in the muscle of each of the patients was noted, with the average decrease equalling 6.6 milliequivalents per kilogram of fat-free tissue. There was also a decrement of the sodium content of the tissue which equalled 9 milliequivalents per kilogram. A definite decrease in the potassium content of the tissue occurred in each of the patients and averaged 8.6 milliequivalents per kilogram of fat-free tissue. The quantity of potassium lost fluctuated from 6.2 to 13.5 milliequivalents per kilogram of fat-free tissue.

In order to rule out influences due to alterations of hydration which would affect measurements of the muscle electrolyte content, the concentrations of chloride, sodium, and potassium per 100 grams of *fat-free solids* were determined (Table VI). Since the muscle solids remained rather constant during the short periods of these experiments and are not affected by alterations of the extracellular phase, expressions of muscle electrolytes in

TABLE IV.—EFFECTS OF WITHDRAWING GASTRIC CONTENTS UPON BODY WEIGHT, TOTAL BODY WATER, PLASMA VOLUME, AND INTERSTITIAL VOLUME

Case No.	Weight, kgm.			Total body water, liters			Plasma volume, liters			Interstitial space, liters		
	Normal	Hypochloremia	Balance	Normal	Hypochloremia	Balance	Normal	Hypochloremia	Balance	Normal	Hypochloremia	Balance
1	65	60	−5	39.0	34.5	−4.5	3.0	2.4	−0.6	10	6.4	−3.6
2	55	51	−4	—	—	—	2.8	2.3	−0.5	8.5	6.6	−1.9
3	68	62.5	−5.5	40.5	36.1	−3.4	3.0	2.4	−0.6	11.0	7.7	−3.3
4	70	64.2	−5.8	—	—	—	3.8	3.0	−0.8	10.7	8.5	−2.2
5	68	64.5	−3.5	—	—	—	3.5	3.0	−0.5	9.7	8.0	−1.7

TABLE V.—MUSCLE COMPOSITION OF ELECTROLYTES AS ALTERED BY ASPIRATION OF GASTRIC SECRETION

(MEQ./KGM. FAT-FREE TISSUE)

Case No. Patient		Muscle water	Chloride	Sodium	Potassium
1	Normal	795	28.5	39.4	88.9
L.G.	After aspiration	760	22.1	31.2	81.0
2	Normal	810	29.2	41.7	86.4
C.V.	After aspiration	775	23.0	33.5	80.2
3	Normal	800	29.0	42.6	84.2
B.B.	After aspiration	765	21.4	32.0	75.1
4	Normal	785	27.1	38.8	83.5
J.C.	After aspiration	758	19.5	30.2	76.0
5	Normal	798	28.0	39.9	88.7
M.L.	After aspiration	760	22.6	30.8	75.2

terms of fat-free solids will present the absolute electrolytic changes occurring in the different situations.

A decrease in the chloride content of muscle occurred in 4 of the 5 patients and averaged a net decrease of 4.9 milliequivalents per 100 grams of fat-free solids. The reason for the increase in Case 4 is not known, but in view of the remainder of the data on this patient the figure may be in error.

An average loss of the muscle *sodium* occurred, averaging 6.7 milliequivalents per 100 grams of fat-free solids, and varied from 5.5 to 7.7 milliequivalents.

There was an average loss of 10 milliequivalents of *potassium*. The smallest potassium loss was manifested in Case 4 in which the loss was 7.4 milliequivalents per 100 grams of solids, and the greatest loss occurred in Case 5 in which the potassium depletion per 100 grams of fat-free solids equalled 12.4 milliequivalents. These data demonstrate an absolute loss of tissue chloride, sodium, and potassium.

The distribution of the electrolytes and water within the muscle (Table VI) reveals that extracellular water content decreased an average of 34.8 grams per 100 grams of fat-free solids and varied from 30 to 47 grams. The average intracellular water decrement was also 34.8 grams per 100 grams of fat-free solids. There was no correlation between the extracellular and intracellular water content of the tissues. Thus, in Case 4 a large extracellular water loss of 35 grams per 100 grams of fat-free solids was demonstrated, and 8 grams of intracellular water were lost. Contrariwise, a greater quantity of intracellular water was lost in Case 5 than the extracellular water decrement. The exact explanation for these divergent exchanges is not manifest.

The essential sodium changes consisted of an extracellular decrement which averaged

TABLE VI.—THE EFFECTS OF WITHDRAWING GASTRIC JUICE FROM PATIENTS WITH ANACIDITY UPON THE MUSCLE CONTENT AND DISTRIBUTION OF WATER AND ELECTROLYTES

		Muscle per 100 gm. fat free solids				Distribution within extracellular and intracellular position							
Case No. Patient	Diagnosis	H_2O gm.	Cl mEq.	Na mEq.	K mEq.	(assumed) $(Cl)_i$ mEq. 100 gm. FFS	$(Cl)_e$ mEq. 100 gm. FFS	$(H_2O)_e$ gm. 100 gm. FFS	$(H_2O)_i$ gm. 100 gm. FFS	$(Na)_e$ mEq. 100 gm. FFS	$(Na)_i$ mEq. 100 gm. FFS	$[Na]_i$ mEq. kgm. H_2O	$[K]_i$ mEq. kgm. H_2O
1	Normal	388	13.9	19.2	43.9	1.0	12.9	115	273	16.9	2.3	8	161
L.G.	After aspiration	317	9.2	13.0	33.7	1.0	8.2	85	232	11.7	1.3	6	145
2	Normal	426	15.4	21.9	45.5	1.0	14.4	136	290	20.7	1.2	4	157
C.V.	After aspiration	344	10.2	14.9	35.7	1.0	9.2	89	255	12.1	2.8	11	140
3	Normal	400	14.5	21.3	42.1	1.0	13.5	144	256	19.7	1.6	6	164
B.B.	After aspiration	326	9.1	13.6	32.0	1.0	8.1	112	214	14.9	−1.3	—	150
4	Normal	365	12.6	18.0	38.8	1.0	11.6	105	260	15.3	2.7	10	149
J.C.	After aspiration	322	18.1	12.5	31.4	1.0	7.1	70	252	9.1	3.4	14	125
5	Normal	395	13.9	19.8	43.8	1.0	12.9	121	274	17.1	2.7	10	160
M.L.	After aspiration	317	9.4	12.8	31.4	1.0	8.4	91	226	12.6	0.2	1	139

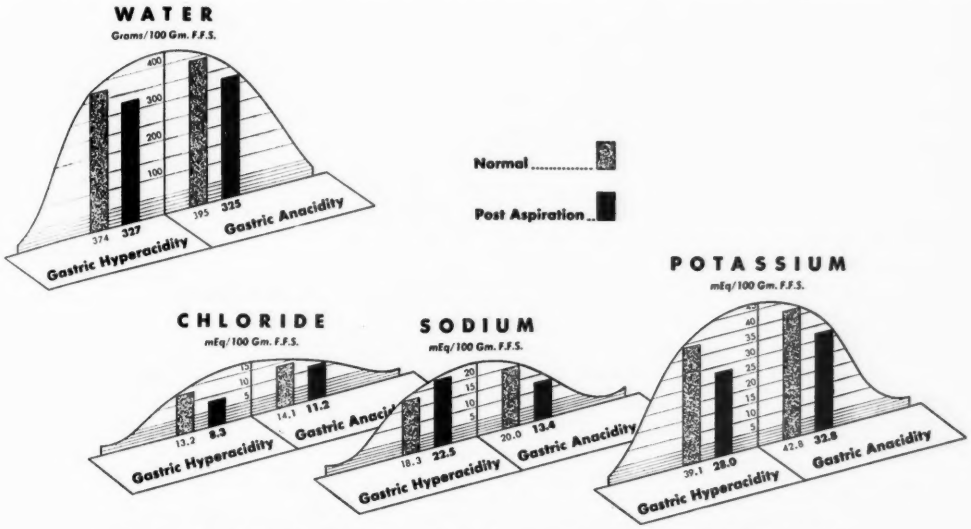

Fig. 2. Effects of gastric aspiration upon muscle composition per 100 grams fat-free solids.

5.9 milliequivalents per 100 grams of fat-free solids and varied from 4.5 to 8.6 milliequivalents. The intracellular sodium increased slightly in 2 patients and decreased in the others.

Alterations in the intracellular electrolyte concentrations expressed as milliequivalent of intracellular sodium and potassium per kilogram of intracellular water show a variable change in the sodium content with an increase in Cases 2 and 4 and a slight decrease in the others. In contrast was the marked decrement of intracellular potassium which equalled 18 milliequivalents per kilogram of intracellular water and fluctuated between 16 and 24 milliequivalents per kilogram of intracellular water.

Discussion

The withdrawal of gastric juice from humans sets off a veritable chain reaction of metabolic alterations which affect the entire fluid and electrolytic structure of the organism.

Loss of total body electrolytes

The essential effect is an absolute loss of sodium and chloride, and to a lesser extent, potassium. The significant quantities of each of these electrolytes in the gastric juice are responsible for the decrement. The diminution in the urinary excretion of sodium, chloride, and potassium as the experiment progresses demonstrates an attempt of the body to conserve these ions. The loss of total body electrolytes prevents the retention of normal quantities of water. In these experiments an attempt was made to avoid the factor of dehydration by administering to each patient ionic-free fluid intravenously in excess of that siphoned out of the stomach. The attempt was unsuccessful and dehydration developed because of the body's inability to retain the administered water which was rapidly excreted (1). This dehydration is manifested by the loss of weight, and a loss of tissue water.

The explanation for the significant quantities of sodium in the gastric juice of these patients is not known. Whereas chloride is secreted into the stomach by the parietal cells during the normal function of making hydrochloric acid, the exact mechanism for the large amounts of sodium bound to the chloride ion within the gastric juice of these patients awaits elucidation. A portion of it most likely enters the stomach through diffusion from the plasma and some may come from regurgitation of intestinal secretions into the stomach. Its

presence in such large quantities results in a total loss of body electrolytes, similar to the electrolytic defect produced in animals by introducing ionic-free water intraperitoneally and subsequently withdrawing the fluid which contains body electrolytes that had migrated into this fluid in answer to osmotic demands. This total loss of electrolytes and the concomitant loss of water frequently results in minor alterations in the concentrations of plasma crystalloids, the result of hemoconcentration, despite the absolute loss of the electrolytes. These minor alterations in concentration may mask the true nature of the defect. Because of the loss of cations in association with the chloride loss, there are often only minor changes in the carbon dioxide combining power. The chloride content of the gastric juice always exceeded the sodium content, although slightly, in the patients herein described. Therefore, the carbon dioxide combining power did rise, and hypochloremia developed as the experiment continued. A hyponatremia developed in each patient. The serum potassium concentrations fluctuated, with a slight decrease in some and a mild increase in others.

Indices showing the direction and magnitude of the electrolytic changes are offered by analyzing muscle for its total water and electrolyte content. Such studies performed in animals have yielded valuable data in understanding electrolyte balance. Studies in humans have been meager because of certain inherent annoyances of the technique. Because of the possibility of specie differences it is essential that such analyses be performed in the human.

Four significant alterations were observed. These were: (1) a loss of muscle water, (2) a decrease of muscle chloride, (3) a decrease of muscle potassium, and (4) a decrease of muscle sodium. By utilizing the premise that practically all of the chloride is in the extracellular space, one can compute the distribution of sodium, potassium, and water between the intracellular and extracellular compartments. An understanding of this distribution is of great importance in devising repair solutions. If a defect is exclusively extracellular, it is necessary only to administer the proper repair solution to correct the extracellular defect. Since all repair substances are introduced into the extracellular space (hypodermoclysis, venoclysis, or ingestion), it is essential in the presence of *intracellular defects* that the repair substances which are deposited outside the cell boundary will evoke the necessary alterations to correct the intracellular defect.

The utilization of the concept of the extracellular positioning of the chloride ion might be challenged. Recent studies by Deane and his associates have shown that a significant quantity of chloride is intracellular. Overman has demonstrated a breakdown of the selective cell membrane permeability during malaria, and the author has shown the same phenomenon to occur after anoxia and hypotension. However, careful analyses of tissues of normal animals by Manery and Hastings and others have shown that chloride exists in most tissues in the same concentration as an ultrafiltrate of plasma. It may thus be assumed that most chloride is extracellularly positioned, and since there is nothing in these experiments, such as severe fever or anoxia, to disrupt the normal selective permeability functions of the cell membranes, it would appear safe to adhere to the concept of the extracellular position of chloride for these calculations. Even should this concept not be entirely correct, the introduced error would merely be one of magnitude rather than direction of the calculated alterations.

The observation that there is a total loss of electrolytes from the muscle demonstrates a total body loss of both cations and anions. Ordinarily during alkalosis there is an increase in the intracellular sodium. This reaction probably represents an autoregulatory mechanism for the maintenance of intracellular stability. Darrow and associates believe that the high carbon dioxide combining power exerts a regulatory role in determining cationic placement. Cooke has presented evidence to indicate that the intracellular alterations result from changes of hydrogen ion concentration of the extracellular space. Elkinton and associates (6, 7) believe that the transfer of cations across the cell boundary is an expression of the metabolic activity of the cell produced with the expenditure of energy. Where-

as in the usual hypochloremic alkalosis there is an increase in intracellular sodium associated with intracellular potassium depletion, in some of the patients of this investigation there was a loss of both intracellular sodium and potassium. The exact significance of this loss is not known.

CONTRAST OF CHANGES INDUCED IN PATIENTS WITH ANACIDITY AND THOSE WITH HYPERACIDITY OF THEIR GASTRIC CONTENTS

A review of the alterations induced by patients with hyperacidity and those with anacidity of their gastric contents reveals some rather interesting changes (2).

Electrolyte content of the gastric aspirate. Whereas 629 milliequivalents of chloride were withdrawn from the patients with gastric hyperacidity, only 369 milliequivalents were withdrawn from those with anacidity. The sodium withdrawn, however, was much higher in those patients with anacidity (351 mEq.) than in patients with gastric hyperacidity (272 mEq.). The total quantity of potassium aspirated was similar for the two groups (55 and 60 mEq. respectively).

Alterations in the plasma concentration of electrolytes. A profound hypochloremia in patients with gastric hyperacidity developed (an average of 101 mEq./l. dropped to 78 mEq./l.) and a much less intense hypochloremia occurred in those with anacidity of their gastric contents (an average of 97 mEq./l. decreased to 87 mEq./l.). There was a total average plasma loss of 123 milliequivalents of chloride in patients with gastric hyperacidity and an average of 83.5 milliequivalents of total plasma chloride lost in those with gastric anacidity. The higher plasma chloride in patients with anacidity is due to two factors: a smaller decrement of chloride and a greater loss of plasma water (600 ml.) which would tend to concentrate the available plasma chloride. In instances of marked water deprivation this hemoconcentrating effect would completely mask an electrolyte deficiency when only measurements of the electrolyte concentration in the plasma are determined.

The carbon dioxide combining power of the plasma in patients with gastric hyperacidity revealed a severe alkalosis (over 38 mEq./l.).

TABLE VII.—COMPARISON OF THE EFFECTS OF THE COMPOSITION OF GASTRIC JUICE UPON METABOLIC ALTERATIONS IN THE FLUID CONTENT OF ORGANISM INDUCED BY GASTRIC ASPIRATION

	Patients with gastric hyperacidity			Patients with gastric anacidity		
	Normal	After aspiration	balance	Normal	After aspiration	balance
Total body water, liters	36.8	34.1	−2.7	39.7	35.3	−4.4
Body weight, kilograms	59.8	56.1	−3.7	65.1	60.4	−4.7
Plasma volume, liters	3.1	2.7	−0.4	3.2	2.6	−0.6
Interstitial space, liters	9.6	7.9	−1.7	10.1	7.4	−2.7

In those with anacidity a modest increase in the carbon dioxide combining power occurred (average of 28 mEq./l.).

The plasma alterations of sodium diminished in the two groups. This occurs because in patients with gastric hyperacidity there is a shift of sodium into the intracellular compartment and a significant loss of sodium by way of the urine. In patients with gastric anacidity a sodium loss in the gastric aspiration occurs as well as by urinary excretion. The net result is that a similar change in plasma sodium develops, consisting of a rather slight decrease in the plasma content of this ion. There is a total loss of 78 milliequivalents of plasma sodium for the patients with hyperacidity and an average total loss of 110 milliequivalents for patients with gastric anacidity.

A decrease in the plasma potassium from an average of 4.5 to 3.8 milliequivalents per liter occurs in patients with hyperacidity and an insignificant rise from an average of 4.6 to 4.8 milliequivalents per liter occurs in the patients with gastric anacidity. The net result, however, for this group is a total decrement of 2.2 milliequivalents of total plasma potassium, and a similar decrement of 2.1 milliequivalents of total plasma potassium for patients with gastric hyperacidity.

Alteration in total fluid and distribution of fluid (Table VII). In patients with hyperacidity the net loss of fluid equalled 2.7 liters, decreasing from 36.8 to an average of 34.1 liters. The net loss in patients with anacidity aver-

TABLE VIII.—COMPARISON OF THE EFFECTS OF THE COMPOSITION OF GASTRIC JUICE UPON METABOLIC ALTERATIONS IN MUSCLE WATER AND ELECTROLYTES INDUCED BY GASTRIC ASPIRATION

Expressed as gm./100 gm. fat-free solids:	Patients with gastric hyperacidity			Patients with gastric anacidity		
	Normal	After aspiration	Balance	Normal	After aspiration	Balance
Water	373.6	326.8	−46.8	394.8	325.2	−69.6
$(H_2O)_e$	108.2	83.8	−14.4	124.2	89.4	−34.8
$(H_2O)_i$	265.4	243.0	−22.4	270.6	235.8	−34.8
Chloride	13.2	8.3	− 4.9	14.1	11.2	− 2.9
$(Na)_e$	15.9	11.5	− 4.4	18.0	12.1	− 5.9
$(Na)_i$	2.6	11.0	+ 8.4	2.1	1.5	− 0.6
Expressed as mEq./kgm. of water:						
$[Na]_i$	11.7	38.2	+26.5	7.8	6.1	− 1.7
$[K]_i$	147.0	115.2	−31.8	158.0	140.0	−18.0

Subscript "e" means "extracellular." ( ) means total amount.
Subscript "i" means "intracellular." [ ] means concentration.

aged 4.4 liters, decreasing from 39.7 to 35.3 liters. These losses are reflected in a decrease in the patients' weights which averaged 3.7 kilograms for those with hyperacidity and 4.4 kilograms for those with anacidity. The average plasma volume decrease was 0.4 liter in patients with a high free acid content and 0.6 liter for those with a low free acid content. The interstitial volume diminished 1.7 liters for patients with hyperacidity and 2.7 liters for those with anacidity.

Urinary excretion of electrolytes. A comparison of urinary content of electrolytes in the two groups of patients revealed that the urinary chloride dropped precipitously in patients with hyperacidity (18.5 mEq. during the first half of the experiment and 4.0 mEq. during the second half of the experiment) as the gastric aspiration continued but decreased more slowly in patients with anacidity (from 11.7 to 9.5 mEq.). In patients with hyperacidity the average sodium (20.3 to 53.1 mEq.) and potassium (25.8 to 77.1 mEq.) contents of the urine increased markedly as gastric aspiration continued, whereas in those with anacidity the increase in the content of these electrolytes did not occur. (Na 13.5 to 15.3 mEq. and K 13 mEq. during both periods.)

Alterations in muscle water and electrolytes (Table VIII). In patients with hyperacidity of the gastric juice there was a net loss of 46.8 grams of water per 100 grams of fat-free solids. The average water decrement is much greater in patients with gastric anacidity, averaging 69.6 grams per 100 grams of fat-free solids. The average extracellular decrease equaled 14.4 grams per 100 grams of tissue in patients with gastric hyperacidity and more than doubled this quantity in patients with anacidity, averaging 34.8 grams per kilogram. The intracellular water decreased an average of 22.4 grams per kilogram in patients with gastric hyperacidity less than the 34.8 grams per kilogram in patients with gastric anacidity.

An average of 4.9 milliequivalents of chloride was lost from the muscle in patients with increased acid in the stomach contents, while those with a low quantity of gastric acidity lost 2.9 milliequivalents of chloride.

The decrease in the extracellular sodium is similar in the two groups. However, there is a significant rise in the intracellular sodium in the patients with gastric hyperacidity and a slight decrease in those with gastric anacidity (Table VIII).

When the quantities of the tissue electrolytes are expressed in terms of their concentration per kilogram of cellular water, rather profound changes are observed. In patients with gastric hyperacidity the intracellular sodium increases an average of 26.5 milliequivalents whereas in those with gastric anacidity it diminishes 1.7 milliequivalents per kilogram of intracellular water.

The tissue potassium changes are significant. In patients with gastric hyperacidity there was an average loss of 31.8 milliequivalents per kilogram of intracellular water and in those with gastric anacidity there was an average loss of 18 milliequivalents per kilogram of intracellular water.

SUMMARY OF COMPOSITION OF GASTRIC ASPIRATE AS IT AFFECTS METABOLIC ALTERATIONS

The essential changes between the two groups of patients depend upon the sodium content of the gastric aspirate. In patients with gastric hyperacidity the loss of chloride

in excess of sodium produces a series of changes which consist of hypochloremia, alkalosis, and decrease in total body water with the interstitial space contributing greatest to this loss. The hypochloremia with resultant alkalosis is apparently a strong stimulus to the development of potassium deficiency which in turn converts the hypochloremic alkalosis to a hypokalemic alkalosis. In the muscle biopsies a rather significant increase in the intracellular sodium occurs, apparently the result of the autoregulatory mechanism in response to the potassium deficiency and metabolic alkalosis.

In contrast, the essential changes produced in patients with gastric anacidity consist of total loss of sodium, chloride, and water. This loss of a complete salt produced an electrolyte deficiency and the corresponding shrinkage of the organism's water volume. Because there is a simultaneous loss of electrolytes and water, rather severe defects may develop before they will be reflected by changes in the crystalloid concentration of the plasma. If sodium and chloride were removed in equal quantities, electrolytic neutrality would be maintained and there would be no compensatory mechanisms retaining carbon dioxide, with the resultant production of metabolic alkalosis. This occasionally occurs and patients may lose large quantities of gastric contents with very little if any increase in plasma carbon dioxide combining power. However, since there is usually some excess of chloride over sodium within the gastric aspirate, a variable retention of carbon dioxide will occur and the degree of alkalosis produced will depend essentially upon the chloride-sodium differential of the gastric juice. In each of the patients studied the alkalosis was relatively mild and it developed more slowly than in patients with gastric hyperacidity.

Summary and Conclusions

The withdrawal of gastric juice from patients with gastric anacidity produces a series of metabolic alterations which result essentially from the removal of a complete electrolyte (chloride and sodium).

When gastric juice was aspirated from 5 patients with gastric anacidity for a period of 4 to 6 days, an average of 369 milliequivalents of chloride (varying from 297 to 518 mEq.) and 351 milliequivalents of sodium (varying from 280 to 487 mEq.) was aspirated. The average quantity of potassium aspirated equalled 60 milliequivalents.

The essential serum electrolyte changes consisted of a decrease in the serum chloride, a limited rise in the carbon dioxide combining power, and a diminution of the serum sodium content. There was a concomitant reduction of the total body water which resulted in concentration of the body electrolytes. The net change was a slight decrease in the concentration within the serum despite rather significant losses of electrolytes from the organism.

Inasmuch as sodium, as well as chloride, was lost from the gastric aspirate, a marked rise in the carbon dioxide combining power did not occur.

A significant loss of water occurred and if water replacement was attempted without the simultaneous administration of electrolytes, the administered water could not be retained and a dehydration of depletion occurred. This was manifested by an average decrease of 4.8 kilograms of body weight, a loss of approximately 4 liters of total body water as determined by deuterium dilution, a loss of 0.6 liter of plasma, and a diminution of 2.5 liters of interstitial fluid.

The alteration in the muscle electrolytes and water revealed a significant diminution in muscle water, muscle chloride, muscle sodium, and muscle potassium. The significance of these muscle alterations are discussed.

Patients with *gastric hyperacidity* who lose chloride in excess of sodium by gastric aspiration develop a marked alkalosis and severe hypochloremia. It appears that the hypochloremia in some manner stimulates the excretion of potassium so that the resultant changes are hypochloremia, alkalosis, and potassium deficiency. These alterations can usually be diagnosed rather easily by analyses of plasma electrolyte concentration. The converse pertains in patients with *gastric anacidity*. Because of the loss of a whole salt and a resultant dehydration the hemoconcentration tends to negate determinations of the effects of the electrolyte loss. If measurements of the defect are attempted by analysis of the concentration

of plasma electrolytes alone, the results will often be misleading.

A comparison of the effects of gastric aspiration in patients with gastric hyperacidity and in those with anacidity are presented and their clinical significance is discussed.

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A QUANTITATIVE STUDY OF THE "AZYGOS FACTOR" DURING VENA CAVAL OCCLUSION IN THE DOG

MORLEY COHEN, M.D., and C. WALTON LILLEHEI, M.D., F.A.C.S., Minneapolis, Minnesota

TOTAL occlusion of the venous inflow to the heart has been utilized both experimentally and clinically to permit intracardiac procedures of short duration. The tolerance of the canine heart to acute complete interruption of blood inflow has been the subject of an earlier report by the authors (4). It was stressed that the major limitations of the method were primarily cerebral rather than cardiac, and although the majority of the animals survived 7 minutes of total inflow stasis, evidence of central nervous system damage appeared after a period of 4 or 5 minutes. Puppies could withstand somewhat longer periods of total vena caval occlusion before the same effects could be noted.

The work of Schiebe and associates has shown that the kidney will withstand complete interruption of its circulation for up to 2 hours with recovery. It has been demonstrated by Weslowski and co-workers that the canine myocardium can survive as much as 30 to 60 minutes of acute total ischemia. The liver is far more sensitive to complete arrest of its circulation as has been shown recently by Raffucci. In fact, it is quite likely that both the brain and liver are far more susceptible to anoxic damage than is the heart itself.

The question arises as to how much blood the vital organs need, as well as to what extent they are capable of withstanding temporary reduction of the major portion of their total blood supply without discernible sequelae. These questions have immense practical importance in the development of suitable techniques for intracardiac surgery. In a recent experimental study Andreason and Watson have stressed the existing confusion in the literature with regard to the effects of total occlusion of the venous inflow to the heart; particularly as to whether the azygos vein was occluded or was permitted to drain into the right auricle during the period of occlusion. The significance of this point was further borne out by the fact that dogs would withstand prolonged periods of inflow occlusion when the azygos vein was not ligated, and the azygos blood was thus allowed to enter the heart during the period of occlusion of the superior and inferior venae cavae. In their study they measured the azygos vein flow during vena caval occlusion employing an electromagnetic flowmeter, but they did not correlate this flow with the size of the animals employed. It was pointed out by them that normally the azygos vein flow, in spite of the apparent size of the vein, is rather low, but immediately after occlusion of the venae cavae the azygos flow increased fivefold or more.

Preliminary experiments in our laboratory had indicated to us that dogs survived remarkably well for long periods of time with both venae cavae occluded temporarily but with the azygos vein unligated so that its flow could drain into the right atrium. Thus, it was apparent that the amount of blood that flowed through the azygos vein under such conditions was sufficient to maintain the vital organs undamaged. This conclusion was surprising to us, but nonetheless inescapable. Therefore, the present study was undertaken in order to measure directly the amount of this azygos flow in a substantial series of animals during an arbitrary period of 30 minutes of caval occlusion. Observations were also made on mean systemic blood pressure and pulse rate during these periods. All animals in the series were subjected to complete autopsy examination at the conclusion of these studies.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis.

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Dr. Cohen is a Life Insurance Medical Research Fellow.

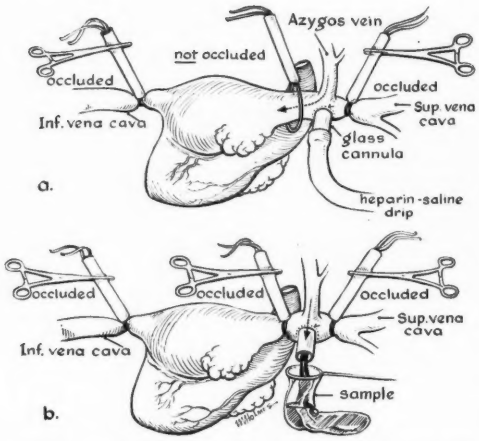

Fig. 1. Method of study. a, Determining survival with azygos vein flow maintained but with both venae cavae otherwise occluded. b, Collecting of 20 second sample to determine quantity of azygos flow when both venae cavae are occluded.

METHOD OF MEASURING AZYGOS VEIN BLOOD FLOW DURING VENA CAVAL OCCLUSION (FIG. 1)

Unselected healthy mongrel dogs of approximately serial weights were employed in the study. The anesthesia consisted of a preoperative dose of morphine sulfate (4 mgm. per kgm. body weight), plus intravenous sodium pentothal employed as a 2.5 per cent solution (25 mgm. per kgm. body weight) administered in fractional doses. This type of anesthesia was superior to pentobarbital because respiratory depression was not as severe at the conclusion of the procedure. All animals were intubated with a cuffed endotracheal tube and manually respirated with 100 per cent oxygen employing a closed system containing a standard carbon dioxide absorber.

By utilizing sterile technique and with the right chest uppermost, the fourth intercostal space was opened. The superior vena cava was dissected up and a loop of umbilical tape passed around it well above the azygos vein. A second loop of tape was passed around the intrapericardial superior vena cava below the azygos. The inferior vena cava was similarly looped with tape just proximal to its entrance into the right atrium. The free ends of each of the 3 loops of tape were then threaded through a short length of rubber tubing. By pulling up on the tapes and sliding the tubing down against the vena cava, a rapid and effectual occlusion could be obtained and maintained by clamping across the rubber tubing with a hemostat. Prior to the start of the experiment the azygos vein was also carefully dissected out and occluded with an atraumatic bulldog clamp. Then when the tapes around the superior vena cava above and below the azygos were occluded, a bloodless segment of vena cava at the level of the azygos vein was obtained. A short wide glass cannula (secured with a length of flexible mechanics' wire to permit handling from outside the chest cavity, Fig. 2) was then purse-stringed into this segment of superior vena cava on its anterior wall opposite to the orifice of the azygos vein. The free end of this cannula was connected to a slow drip of sterile normal saline containing 5 milligrams of heparin per 100 cubic centimeters to maintain its patency until the time the actual measurements were made (Fig. 1a), as well as during the interim when measurements of the azygos flow were not being made. When the cannula was secured in position, the occlusive tapes about the vena cava and the bulldog clamp on the azygos vein were released, thus permitting a free flow of blood into the right auricle in the normal manner until such time as the measurements described in the following were made.

To collect and measure the azygos flow during the periods of venae cavae occlusion, a commercial condom previously tied to a flexible wire frame was employed (Fig. 1b). The condom, after being rinsed in a heparin saline solution, would lie flat in the anterior mediastinum below the level of the azygos, and in this way neither gravity nor siphonage would interfere with the flow during the periods of collection.

A stop watch was used for time measurements, and the uppermost tape on the superior vena cava and the one on the inferior vena cava were occluded. After 2 minutes, the tape around the intrapericardial superior vena cava below the entrance of the azygos vein was also occluded and the heparin saline drip disconnected. A few seconds were allowed to

elapse to permit the flow to stabilize. Then the mouth of the condom was placed beneath the open end of the cannula and the flow from the azygos vein collected for 20 seconds. At the conclusion of this period the intrapericardial tape was released and the saline drip reconnected—the main caval occlusion being maintained as illustrated in Figure 1a. Thus the animal was being maintained entirely by the quantity of blood entering the heart via the azygos vein. Similar direct collections of the azygos flow for 20 second periods were made at 12, 22, and 30 minutes of caval occlusion. As each azygos flow sample was obtained it was carefully measured in a graduate and then slowly returned to the dog by injection through the tubing of the saline drip. Blood pressures were recorded with a mercury manometer introduced into the femoral artery, permitting mean pressures to be read at intervals throughout the procedure. After 30 minutes the tapes on the inferior vena cava and on the superior vena cava cephalad to the azygos vein were released. Before the chest was closed, the hole in the superior vena cava left by removal of the cannula was repaired with No. 6–0 arterial silk. The animals were then allowed to survive for intervals up to 5 weeks in order to observe any sequelae of the reduced blood flow. Postoperatively all animals received a daily intramuscular injection of 300,000 units of penicillin and 0.5 gram of streptomycin for 3 days. They were observed daily for any abnormal behavior until their sacrifice.

A total of 19 animals were utilized in this study. In 17 of these, flow measurements were carried out as already outlined. In these 17 dogs it is perhaps apparent, and mentioned here for clarity, that during the 30 minutes of caval occlusion all of the 17 animals were maintained only on their azygos flow; but, in addition, during the periods of actual measurement of the azygos flow (20 seconds), these animals had no blood entering the heart at all. Thus this method was a slightly more severe test than would have been obtained had the animals been allowed to exist on their azygos flow without direct measurements being made—as was done in the remaining 2 animals of this group in which the venae cavae were occluded for the 30 minute interval with the azygos vein open, no flow data being recorded.

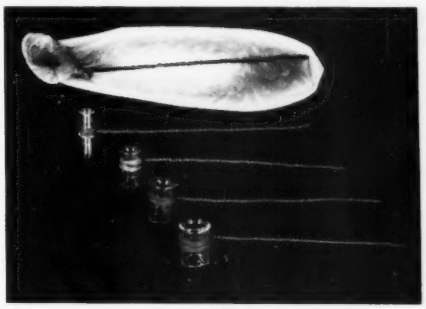

Fig. 2. Cannulas and condom for collecting azygos flow samples.

RESULTS

The overall results of the 30 minute occlusion of the venous inflow with the azygos open are shown in Table I. It will be seen that none of the animals died during the 30 minutes of complete vena caval occlusion with the azygos vein open. Two dogs (Nos. 667 and 1134) died on release of the inflow as a result of ventricular fibrillation. As in the earlier study (4), no attempts were made at cardiac resuscitation in these 2 animals. Dog No. 331 survived occlusion but manifested moderately severe central nervous system damage. This occurrence is quite likely the result of a technical error during the procedure which occurred when the blood clotted in the collecting cannula and in the superior vena cava. As a result, the azygos inflow was almost completely obstructed in this particular dog for a 10 minute interval, this condition not being noticed or corrected until the next sample was drawn. However, it is evident from these studies that at least 16 of 19 dogs, or approximately 84 per cent of the animals, safely survived, without demonstrable ill effects, 30 minutes of reduction of cardiac inflow to the amount flowing through the azygos vein during that period.

Thus, the amount of blood flowing through the azygos vein during occlusion of both of the venae cavae is of considerable significance. These measurements of this azygos flow are

TABLE I.—RESULTS OF 30 MINUTES OF COMPLETE VENA CAVAL OCCLUSIONS WITH AZYGOS VEIN OPEN

Dog No.	Immediate result		Delayed result
	Survival	Death	
*1201	+		Sacrificed 14 days; no pathology
*1134		+[1]	
1746	+		Sacrificed 12 days; no pathology
110	+		Sacrificed 14 days; no pathology
1595	+		Sacrificed 14 days; no pathology
632	+		Sacrificed 16 days; no pathology
1527	+		Sacrificed 13 days; no pathology
667		+[1]	
540	+		Sacrificed 29 days; no pathology
393	+		Sacrificed 8 days; no pathology
1338	+		Sacrificed 17 days; distemper
636	+		Sacrificed 15 days; no pathology
331	+		Blindness and spacity; sacrificed 3 days—unimproved[2]
1164	+		Sacrificed 11 days; no pathology
679	+		Sacrificed 34 days; no pathology
589	+		Sacrificed 4 days; no pathology
1600	+		Sacrificed 16 days; no pathology
1624	+		Sacrificed 10 days; no pathology
1793	+		Sacrificed 16 days; no pathology

*No flow measurements carried out.
[1]Both deaths resulted from ventricular fibrillation immediately upon release of the vena caval clamps after conclusion of 30 minutes of occlusion. No attempt made to defibrillate.
[2]Technical difficulties due to clotting in the caval cannula may account for this result.

shown in Table II. Certain features are apparent upon examination of these data. Consistently, and within the accuracy of the method, the first readings of the azygos flow made at 2 minutes after vena caval occlusion had the largest values. In the ensuing 28 minutes of the occlusion period there was no consistent pattern of variation. In some instances the measurements at 22 minutes were greater than at 12 minutes (Nos. 1746, 632, 331). In the case of dog No. 667, which died of ventricular fibrillation that occurred at the time of release of the main caval occlusion, it may be seen that there was an unusually marked fall in the azygos flow (more than half the initial value) during the 30 minute occlusion. Presumably myocardial efficiency had been impaired to such an extent during this period of reduced flow that the heart was unable to "take over" upon release of the venae cavae. This explanation gains some support from earlier experience in total inflow occlusion studies (4), where it was noted that the release of the venae cavae successively rather than simultaneously, in large measure, prevented the severe degrees of cardiac dilatation that occurred in many instances. Whether or not the other death in the series (No. 1134) was related to a markedly reduced azygos flow can only be inferred as the flow was not measured in this instance.

The variability of the azygos flow values during the period of vena caval occlusion is in some disagreement with the findings of Andreason and Watson, who using an electromagnetic flowmeter noted a consistent progressive decline of flow in the 1 dog cited in their paper. It is difficult to explain this discrepancy other than by a difference in methods and the greater number of animals in which the measurements were made in this study. It was noticed in many instances during these studies that by observation the heart action appeared as good at the end of the 30 minute period of occlusion as it did after 15 or 20 minutes. In these animals the flow measurements usually approximated the initial values taken at 2 minutes. On the other hand, in those animals in which the flow at 22 minutes had shown a significant drop from the initial measurement, irregularities of rate and rhythm were not uncommon. Furthermore, the mean blood pressures generally correlated well with the azygos flow value.

An attempt was made to relate azygos flow to body weight. All animals were carefully weighed on a springless scale after being given an adequate preoperative dose of morphine. In this way errors up to 1.2 kilograms resulting from food and excreta were avoided. The flow values were plotted against body weight and the results are shown graphically in Figure 3. The plotted values for flow in each instance were the amount after 2 minutes, as this was considered the optimum value. It will be seen that in larger dogs the azygos flow increased out of proportion to the increase in body weight. Also, the two lowest points on the graph were of results in puppies. Here

TABLE II.—AZYGOS VEIN FLOW DURING COMPLETE VENA CAVAL OCCLUSION

Dog No.	Flow in c.c./min.			
	2 min.	12 min.	22 min.	30 min.
1746	186	156	174	183
110	36	36	33	36
1595	171	144	135	129
632	114	60	69	117
1527	303	270	258	240
667	105	84	66	51
540	63	60	53	36
393	126	—	105	75
1338	201	204	192	189
636	74	74	63	58
331	75	60	75	60
1164	87	81	60	54
679	99	72	72	60
589	297	276	258	234
1600	207	198	192	183
1624	42	33	30	33
1793	189	150	144	132

the flow was likewise greater than expected from the middle portion of the curve; however, this may be due to the fact that in immature animals the heart weight and size are greater per unit of body weight than in the mature animal of an average nutritional state.

Records of mean femoral artery pressure were made during the periods of maintenance on the azygos flow. Prior to the vena caval occlusion, the blood pressure ranged about 100 millimeters of mercury. Immediately on occluding the venae cavae (with the azygos vein open), the pressure fell precipitously to a level between 30 to 40 millimeters of mercury. From this level onward, the trend was that of a progressive decrease, but not invariably so. In those instances in which the flow decreased rather markedly during the initial half of the occlusion period, the blood pressure fell to levels of 10 to 15 millimeters of mercury but rose again as the flow increased during the latter portion of the occlusion. There was, therefore, a fairly close correlation between the amount of blood flowing through the azygos vein and the mean systemic blood pressure. However, in all animals maintained

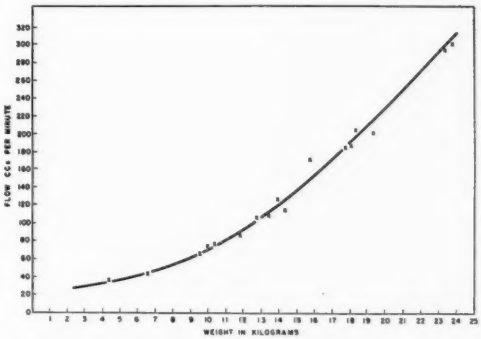

Fig. 3. Relationship of azygos vein flow to body weight during complete vena caval occlusion.

on their azygos flow only, the mean systemic blood pressure was below 50 millimeters of mercury. Upon release the blood pressure immediately rose to a mean of 70 to 75 millimeters of mercury, and within 3 to 5 minutes returned to control levels.

The rate and rhythm of the heart were observed through the open chest. In most instances there was a moderate tachycardia (160 per min.) during the occlusion period. The characteristic changes of rate observed during total inflow occlusion and previously described (4) were not observed. Abnormalities of rhythm were unusual and consisted mainly of extrasystoles occurring during the latter one-third of the 30 minute interval or immediately after release of the inflow. In addition to the 2 cases of ventricular fibrillation noted before, there was only 1 instance of auricular fibrillation and heart block which reverted spontaneously to normal rhythm as chest closure was begun. Spontaneous respirations occurred in all survivals before the experiment was completed.

DISCUSSION

It is obvious from these experiments, as well as those previously reported by us in reference to total (4) and intermittent (8) vena caval occlusion together with the studies of Andreason and others, that the vital organs of the body may be completely and safely maintained functionally with blood flows of far less magnitude than those which they normally receive, even in the resting state.

Moreover, it would appear that, by coincidence or otherwise, the amount of blood flow through the azygos vein (with the inferior vena cava occluded at the heart and the superior cava occluded just cephalad to the azygos vein junction) closely approximates the minimum blood flow which under conditions of normal body temperature and general anesthesia is capable of maintaining the vital organs of the dog functionally intact without detectable organ damage.

Reference to Figure 3 and Table II indicates that in most instances the azygos flow under these conditions amounted to approximately 8 to 14 cubic centimeters[1] of blood per kilogram body weight per minute. These figures may be compared with the generally accepted basal cardiac output of the anesthetized dog which is 165 cubic centimeters per kilogram per minute.

We may speculate further as to the basis underlying the remarkable ability of such vital organs as the brain, liver, and heart to tolerate successfully this massive reduction in their total blood flow.

In this regard some of the experimental work previously reported in the literature may be pertinent. Kety and Schmidt, in their studies of factors controlling cerebral blood flow in man, demonstrated that inhalation of 5 to 7 per cent carbon dioxide resulted in an average increase of 75 per cent in cerebral blood flow. Hilton and Eichholtz, and Markwalder and Starling found that the administration of carbon dioxide resulted in coronary dilatation. More recently, Eckenhoff, Hofkenschiel, and Landmesser have carried out actual coronary flow studies in the dog, and although they were unable to find any consistent alteration in coronary blood flow employing 5 to 7 per cent carbon dioxide, they did demonstrate significant increases in coronary circulation when hypoxia and lowered blood hydrogen ion concentration were induced. In addition in their experiments, epinephrine, in small doses, induced an average increase of 35 per cent in coronary blood flow without significant changes in pulse rate or blood pressure. Others have also confirmed the finding of an enormously increased coronary blood flow coincident with hypoxia or with the administration of sympathomimetic agents such as epinephrine and neosynephrine. Employing simultaneous measurements of coronary blood flow and cardiac output, Eckenhoff and associates were able to show significant increases of coronary blood flow during shock. Still another potent factor in augmenting coronary flow in their study was the accumulated products of local metabolism. In this regard carbon dioxide has been considered by Carlson and coworkers to be one of the most important chemical regulators in the body because of its effects upon blood vessels, blood flow, and respiration. Apparently then, at least several factors can operate to insure a proportionally greater blood supply to the heart and other vital organs in times of circulatory stress. As regards the cerebral and coronary circulation in both animals and man, the products of chemical metabolism and oxygen lack have been clearly established as dominant factors in their intrinsic control.

Beck, in his experimental studies on reduced coronary flow, has repeatedly stressed the importance of the concept of a "trigger" mechanism inducing ventricular fibrillation if sudden reductions of blood flow were produced to localized areas of the myocardium. In contrast, when the main coronary arteries were partially occluded and the reduction of flow was thus generalized over the entire myocardium, the mortality was significantly lower even though the magnitude of the reduction was very great. In this latter circumstance the factor of localized ischemia acting as a trigger mechanism was absent. Although our own studies are not strictly comparable, the reduction of coronary flow which occurs during inflow occlusion (with the azygos vein open) presumably affects the whole heart in a generalized manner and possibly, therefore, small localized areas of ischemic myocardial muscle are not created. These circumstances could conceivably account for the absence of any significant disturbances of cardiac rhythm during the occlusion period.

[1]This figure is exclusive of the return coronary flow which in the closed heart constitutes an internal recirculation augmenting the minimal amounts of measured blood entering the heart from the azygos vein. More recent work in the open heart has shown this internal recirculation factor under these conditions to amount to about 1.5 to 3.0 cubic centimeters per minute per kilogram body weight.

A second important factor compensating for major quantitative reductions in blood flow to organs or structures is an increase in their coefficient of oxygen utilization, i.e. an increase in the quantity of oxygen abstracted from a given volume of blood. In passing through the capillaries the blood under ordinary circumstances loses only a fifth to a quarter of its contained store of oxygen so that the hemoglobin in that blood returning to the lungs frequently has an oxygen saturation of from 75 to 80 per cent. In these studies in which the cardiac output is severely curtailed, the blood flow through the dilated capillaries under low pressure is undoubtedly slower, a greater surface area of capillary endothelium is exposed for diffusion of oxygen, the distance for diffusion of oxygen is shortened by opening up of more capillaries and so reducing the radius of the cylinder of tissue supplied by each capillary, the oxygen tensions within the tissue cells are lower resulting in a steeper gradient for diffusions, and, finally, the action of the acids (carbonic, pyruvic, and lactic) present accelerates the decomposition of oxyhemoglobin. All of these factors favor a far greater extraction by the tissues of the available oxygen in a given quantity of blood. The magnitude of these compensatory mechanisms (all of which occur normally, for example during muscular exercise) is indicated by some studies now in progress in our laboratory wherein, under these conditions of greatly reduced cardiac output, the arterial blood entering these vital organs is normally saturated and customarily contains 19 to 21 volumes per cent of oxygen. But in contrast to what is observed under normal conditions, the venous outflow often contains less than 2 volumes per cent oxygen. These determinations constitute objective evidence of the greatly increased efficiency of oxygen utilization which in effect, under these conditions, permits 100 cubic centimeters of blood to supply the tissues with approximately the same amount of oxygen customarily supplied by 300 cubic centimeters of blood under conditions of normal cardiac output.

A third important compensating factor, and perhaps one of the most important in regard to the ability of the heart to tolerate a significantly reduced coronary flow, as demonstrated in these experiments, is the fact that the work of the heart has been reduced commensurately or even to a greater degree than its coronary flow. To carry this line of reasoning even further, the demonstrated ability of the myocardium to survive in certain instances for 60 minutes without any blood flow at all is most likely a manifestation of the fact that during this period the myocardium was relieved of all external work, and thus survivals could occur for phenomenal lengths of time.

In summary, based upon the foregoing brief review together with certain established physiologic principles relative to the transport and delivery of oxygen to the tissues, a threefold explanation may be suggested for the observed ability of the brain, heart, and liver to tolerate prolonged periods of reduced blood flow without observable functional impairment.

First, under these conditions of enormously decreased systemic cardiac output, the blood flow to these vital organs is not proportionately decreased. This favorable occurrence is the result of a compensatory local and regional vasodilatation with a proportionately greater quantity of blood flow through the tissues due to the lowered vascular resistance. The importance of these intrinsic mechanisms (sensitive to the accumulation of chemical products of metabolism, alterations of hydrogen ion concentration, release of epinephrine, and changes in tissue oxygen tension) for the local control of blood flow and for the redistribution of blood flow to vital areas during stressful periods are well substantiated and have already been briefly alluded to. Secondly, there is a substantial increase in the coefficient of oxygen utilization, and, finally, it is quite likely that the reduction of the work load upon certain organs, notably the heart, greatly increases their tolerance to reduced blood flow.

SUMMARY

1. Nineteen dogs were subjected to temporary complete vena caval occlusion except for the blood flow which entered their hearts via the open azygos vein.

2. All of these animals survived 30 minutes of complete vena caval occlusion with only their azygos vein open. Further, in survival

experiments, 16 animals (84 per cent) completely recovered without demonstrable temporary or permanent sequelae from this 30 minute period without the employment of cardiac or other resuscitative measures.

3. In 17 of these dogs the quantity of blood flow through the azygos vein, which maintained these animals while both venae cavae were otherwise completely occluded, was measured and correlated with their body weight.

4. The quantity of this azygos blood flow, which was responsible for maintenance under these conditions of otherwise complete caval occlusion, was 8 to 14 cubic centimeters per kilogram of body weight per minute. This quantity of flow is less than 10 per cent of the generally accepted basal cardiac output for anesthetized dogs (165 c.c. per kgm. per min.).

5. The principal compensatory factors responsible for this demonstrated ability of a high percentage of dogs safely to survive 30 minutes of remarkably reduced blood flow are discussed with particular reference to the vital organs—the brain, liver, and heart.

6. These compensatory factors are as follows: a proportionately greater blood flow to the vital organs brought about by a local and regional vasodilatation due to certain intrinsic mechanisms for the redistribution of blood flow. These mechanisms are sensitive to the effects of accumulation of chemical metabolites, alterations of hydrogen ion concentration, carbon dioxide accumulation, changes in oxygen tension within tissue cells, and release of epinephrine. Other important compensating factors are the greater efficiency of the tissues in extracting the blood-contained oxygen as manifested by a substantially increased coefficient of oxygen utilization; and in particular reference to the heart, the favorable effect of the reduction in the cardiac work load coincident with and commensurate with (or possibly even exceeding) the reduction in its coronary flow.

7. It would appear that the azygos flow (with the inferior vena cava occluded at the heart and the superior cava occluded just cephalad to the azygos junction) is very close to the minimum requirements at normal body temperature for the maintenance of the vital organs in a temporary state from which full functional recovery may be anticipated.

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THE CASE FOR OPERATIVE CHOLANGIOGRAPHY

CHARLES D. SHERMAN, JR., M.D., and SAMUEL J. STABINS, M.D., F.A.C.S.,
Rochester, New York

DELAYED cholangiography is now a well accepted and established useful procedure. Sporadic enthusiasm has been shown toward operative holangiography, but despite the numerous eports of its value it has failed to become standard procedure when common duct exloration has been undertaken. Our experince at The Genesee and The Strong Memoal Hospitals parallels that recorded in the ecent literature indicating that many stones re left in the common ducts even after thorugh exploration. In the light of our experince and that of others, why has operative holangiography not found its rightful place biliary surgery? We believe that lack of xperience in the procedure and in the interretation of the films combined with the initial ifficulty in joint preparation by those directly oncerned are without doubt the basic reasons r this failure. We do not believe that these actors should restrain the intellectually honst surgeon from giving his patient the benefits o be derived from operative cholangiography. Our axiom is that if there is an indication for exploration of the common duct the same indication holds for operative cholangiography.

Delayed cholangiography and injections of external biliary fistulas date back as far as 1918. Operative cholangiography seems to have been first utilized by Mirizzi as reported by him in 1932. Since Mirizzi's report there have been numerous publications dealing with its direct value in various types of biliary and pancreatic disorders whether calculous, neoplastic, inflammatory, or dyskinetic. Indirectly it has stimulated investigation in pharmacology, physiology, physiopathology, and anatomy. As a result of our own experiences we believe its greatest value by far is in the recognition of common duct stones.

There are several factors in operative cholangiography which deserve some comment.

From the Department of Surgery, Genesee and Strong Memorial Hospitals, Rochester, New York.

1. *Is there really a need for operative cholangiography?* Even the most experienced surgeon to his chagrin has found at times that stones have been left in the common duct despite the most thorough exploration. Judd, in 1931, reporting on 1,608 patients in whom common duct stones were found, stated that 2.5 per cent returned for reoperation and removal of stones. Lahey, in 1933, reported that at least 1 patient in any 10 cases of gallstones had stones left in the common or hepatic ducts following surgery. This would suggest a much higher incidence of residual stones than 2.5 per cent since, as is well known, many small stones will pass, some are asymptomatic, and many patients might have been reoperated on elsewhere. Mixter in 1938 reported that 20 per cent of a group of 41 patients, who were explored for common duct stones and did not have operative cholangiography, had residual stones which were shown on delayed cholangiography.

Two cases illustrating residual stones are presented below.

CASE 1. F.L., female, age 66 years, was admitted to The Strong Memorial Hospital on August 3, 1952 with a 15 year history of chronic gallbladder disease without a history of jaundice. Operation was performed on August 5, and several stones were removed from the common duct. Operative cholangiogram was not done but delayed cholangiogram (Fig. 1) 7 days later revealed several residual stones necessitating a secondary operation on August 12. At that time 4 residual stones were recovered and needless to state an operative cholangiogram (Fig. 2) was requested by the surgeon at this time. This showed no further stones and the operation was completed.

CASE 2. M.L., female, age 59 years, was admitted to the Park Avenue Hospital on February 12, 1948 because a delayed cholangiogram (Fig. 3) revealed a residual stone following cholecystectomy and the removal of common duct stones 2 months previously. At operation by transduodenal approach an impacted ampullary stone was removed.

These 2 cases illustrate that the surgeon cannot always depend on his findings at operation to be certain that all stones have been

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 1. Delayed cholangiogram revealing residual stones.
Fig. 2. Operative cholangiogram on the same patient after removal of stones showing rapid emptying into the duodenum.
Fig. 3. Delayed cholangiogram revealing a residual stone.
Fig. 4. Delayed cholangiogram suggesting a stone. At operation a carcinoma of the ampulla was found.

removed. We believe that operative cholangiography would have prevented the need for a secondary operation with its increased morbidity and mortality risk.

2. *How accurate is operative cholangiography?* To a great extent this depends on the technique used and the interpretation of the films by a competent roentgenologist or surgeon. We have found that, as experience was obtained through more and more cholangiograms, we eliminated air bubbles which are an obvious source of confusion in the interpretation. Another source of inaccuracy may be found with very small stones when the con-

Fig. 5.

Fig. 6.

Fig. 5. Operat ve cholangiogram showing pancreatic reflux.

Fig. 6. Delayed cholangiogram on the same patient after sphincterotomy showing no pancreatic reflux.

Fig. 7. Operative cholangiogram obtained by injecting through a catheter in the cystic duct.

trast media lies in front of and behind the small stone and gives a minimal change in the overall density. A fold in the duct wall has been reported as confusing, but this has not been a difficulty in our experience. Rarely is there difficulty in interpretation between stone and tumor or pancreatitis (Fig. 4). Interpretation of pathologic physiology in our hands has been difficult although others feel more confident in using this means for that purpose. Mixter, reporting on 72 patients who had a normal cholangiogram at the end of operation, stated that none needed reexploration although 2 had mild symptoms not demanding operation. In 41 cases without an operative cholangiogram, 11 showed stones on delayed cholangiogram with reoperation in 4 patients and persisting biliary colic in 5 others.

3. *Does operative cholangiography increase morbidity?* In the literature there are reports of complications such as mild pain and fever which cleared within 2 to 4 days. The rapid disappearance of symptoms suggests a transient cholangitis or pancreatitis secondary to a reflux. However, Martensson in 1946 reported 2 deaths from Escherichia coli infection ascending the biliary tract. We are unaware

Fig. 7.

of any other reports of serious complications. Of about 300 operative and delayed cholangiograms done at The Genesee and The Strong Memorial Hospitals, we have seen very little increase in morbidity although in several instances there was a transient episode of pain associated with a mild febrile reaction. In no instance did we encounter any serious complication. We agree, however, with other observers that complications may be associated with injection of large amounts of dye such as 30 cubic centimeters or more. Usually 5 to 10 cubic centimeters should be adequate.

4. *Is pancreatic reflux of any practical significance?* We believe that pancreatic reflux can be classified into three distinct types.

1. In the presence of obstruction due to calculus at the ampulla pancreatic reflux when present probably has very little significance. With the removal of the obstruction these patients should not have recurring pancreatitis.

2. Reflux without a stone and without a history of pancreatitis indicates to us some mechanical difficulty in injection as too forceful filling of the ducts. We do not expect such patients to have any prolonged difficulties.

3. When there is a history of recurring pancreatitis and reflux occurs, we believe that sphincterotomy offers the best possible method of treatment to date (Figs. 5 and 6).

5. *Can one differentiate carcinoma from pancreatitis in an operative cholangiogram?* There have been reports to suggest that a sharp cutting off of the contrast media indicates carcinoma rather than pancreatitis, the latter showing a gradual decrease in caliber of the duct. Our limited experience does not justify any conclusions in this matter.

6. *Should operative cholangiograms be done in the presence of acute cholecystitis?* Hagan and Townsend in 1948 resorted to operative cholangiograms in acute cholecystitis and found them to be of limited value. Martensson, however, warns of the danger of this procedure and reports 12 cases in which operative cholangiography was done in the presence of acute cholecystitis. In 2 of these instances mild cholangitis developed, and in 7 others "local complications" developed leaving only 3 of the 12 without morbidity. It is safe to assume that a small but definite percentage of patients with acute cholecystitis will have stones in the common duct. We have in no single instance done an operative cholangiogram in this situation although we believe it may be of value if it can be done without increased morbidity.

7. *Should operative cholangiography be done in all cases of elective cholecystectomy associated with stones in the absence of other indications for common duct exploration?* It is well known that in patients with cholelithiasis stones are present in the common duct without causing symptoms or signs as yet. We have done a series of operative cholangiograms using a catheter through the cystic duct without any appreciable time loss or increase in morbidity (Fig. 7). Since it is a benign procedure we do not believe patients should be denied the possible benefit from its use.

8. *Can operative cholangiography obviate exploration of the common bile duct?* In the realization that there is an increased hazard to exploration of the common bile duct every effort should be exerted to prevent unnecessary exploration. The only certain means of avoiding this danger is by operative cholangiography before opening the bile duct. It necessarily follows that in every case in which exploration is considered this procedure should be resorted to. Before concluding we should like to mention that we have used many types of contrast media but we now feel that a recently developed media, mulsopaque, is at least equal to and probably superior to all other media previously used.

CONCLUSIONS

We believe that operative cholangiography is indicated in every case of biliary surgery in which the common duct is explored. We likewise believe that operative cholangiography through the cystic duct should be done in those cases in which exploration is considered.

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GUNSHOT WOUNDS OF THE HIP JOINT

MILTON S. THOMPSON, M.D., F.A.C.S., Colonel, M.C., U.S.A., and
GEORGE E. OMER, JR., M.D., Captain, M.C., U.S.A.,
Fort Sam Houston, Texas

WOUNDS of the hip joint have the highest mortality and the greatest degree of shock of all joint wounds. Battle incurred gunshot wounds are the most severe, and present additional problems of evacuation, complications, and ultimate prognosis. Fischer determined the incidence of gunshot wounds of the hip joint as 9.3 per cent of all wounds and 46 per cent of all joint wounds in three wars of the 19th century. Otis and Huntington reviewed the treatment of 386 cases of hip joint wounds during the American Civil War and found a mortality of 85 per cent. Von Langenbeck reported 132 cases of hip wounds from the Franco-Prussian War and determined mortality as 77 per cent (9). The British official medical history of World War I gives the overall mortality from gunshot wounds of the hip as 60 per cent (7). The official medical history of World War II has not been published, and the present Korean conflict has not ended, so statistics on hip joint wounds sustained are not available; however, it can be stated with considerable certainty, the mortality has been markedly reduced.

CLINICAL STUDY

From January 1949 to March 1953, 24 cases of gunshot wounds of the hip joint were treated by the staff of the Orthopedic Service of Brooke Army Hospital. The ages of the patients ranged from 17 to 58 years. The right hip joint was involved in 14 cases and the left in 10. Nineteen of the wounds were incurred in combat; the other 5 wounds were noncombat wounds resulting from small arms fire with the missile ranging from .32 to .45 caliber. Of the 19 wounded in action, 11 were due to small arms fire and 8 were fragmentation wounds (hand grenade, land mines, artillery shells, and mortar rounds). The length of follow-up of each case varied from 6 months to 34 years, but all cases have reached definite plateaus of response to treatment, and the clinical results can be appraised with adequate accuracy.

The velocity of military rifle and machine-gun bullets, the multiplicity of shell fragments, and the adversity of battlefield conditions combine to produce severe hip joint wounds and associated injuries of bowel, bladder, and other vital structures. Involvement of the sciatic nerve was the most common injury, occurring in 9 cases of the 19 battle-incurred wounds. Fractures other than within the hip joint were found in 8 cases. The gastrointestinal tract was perforated in 5 patients and the bladder was injured in 4 patients.

An analysis of the hip joint wounds was made according to the structures that were damaged within the joint. Capsular injuries were included only when the integrity of the joint was disrupted by roentgenologic evidence (Fig. 1). Involvement of the acetabulum was divided into the inferior (lower) portion of the articular surface (Fig. 2); and the superior (upper) portion of the articular surface (Fig. 3). Wounds involving the femoral neck or head were grouped together (Figs. 4, 5, and 6). Wounds that were not limited to a single component of the joint were classified as combination injuries (Fig. 7).

Sepsis of the hip joint constituted the most common complication. Osteomyelitis did not occur in the 5 noncombat wounds. Sepsis developed in 13 of the 19 combat-incurred wounds; and continued from 5 to 35 months, averaging 10 months per case. The most common organism was hemolytic Staphylococcus aureus, which was cultured in 10 of the 13 septic cases.

From the Orthopedic Service, Brooke Army Hospital, Fort Sam Houston, Texas.

Fig. 1. Wound involving capsule only resulting from small arms fire in 27 year old patient. Roentgenogram 3 years after injury.

Fig. 3. Wound of upper acetabulum and femoral head resulting from small arms fire in 20 year old patient. Roentgenogram 8 months after injury.

Fourteen of the 24 patients have 1 inch or more shortening of the involved lower extremity. The shortening of the extremity can be compared to the proximal migration of the acetabulum of the involved hip joint. The amount of proximal migration was established by comparative measurement of the acetabula from stable anatomic landmarks on the pelvic roentgenograms. Proximal acetabular migration of 0.2 centimeter or more occurred in 14 of the 24 patients.

Measurements of proximal (upper) acetabular migration and the incidence of osteomyelitis provide interesting conclusions relating to prognosis. In 8 cases, the capsule only was injured; 3 of these developed osteomyelitis, but upward migration of the acetabulum did not occur. In 7 cases, the femoral neck and head only were involved; osteomyelitis occurred in 3, but there was no upward migration. In 2 cases, the lower portion of the acetabulum was the sole injury; osteomyelitis followed in both cases, and averaged 1 centimeter migration. The other 7 cases had combined injuries. In 3, the head, neck, and lower acetabulum were damaged; osteomyelitis followed in 2, and migration averaged 2 centimeters. In 4 cases, the head, neck, and upper acetabulum were involved; osteomyelitis was present in 3 cases, and the average upward migration was 3 centimeters.

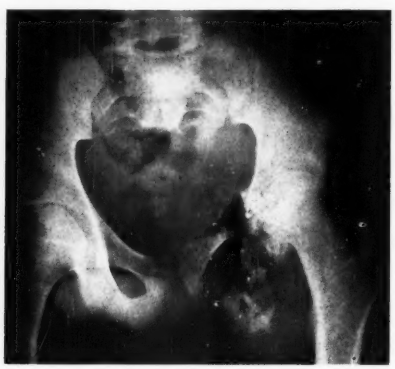

Fig. 2. Wound of lower acetabulum resulting from small arms fire in 20 year old patient. Roentgenogram 6 weeks after injury.

The clinical end results of these 24 patients revealed 13 cases with spontaneous ankylosis or operative fusion of the hip joint, 9 cases with good range of hip motion, 1 arthroplasty, and 1 patient with painful limitation of motion who may later require arthroplasty or arthrodesis of the hip.

Comparison of the clinical end results with the structures damaged within the hip joint revealed that 6 of the 7 combination injuries developed ankylosis and 1 had limited motion that will probably require further surgery. Three of the 7 head and neck injuries had ankylosis; all were complicated by osteomyelitis. Of the 4 remaining head and neck injuries, 3 had good range of motion and the fourth had arthroplasty of the hip 12 years after in-

Fig. 4. Wound of femoral neck resulting from small arms fire in 41 year old patient. Roentgenogram 2 months after injury.

Fig. 6. Wound of femoral neck and head resulting from small arms fire in 27 year old patient. Roentgenogram 1 month after injury.

jury. The 2 acetabular wounds developed osteomyelitis and progressed to fusion. Six of the 8 capsule injuries had a good range of motion, but 2 had ankylosis.

DISCUSSION

In 10 of 13 infected cases, the organism was hemolytic Staphylococcus aureus. Badgley studied 113 cases of spontaneous septic hips and determined that the bacterial organism did not determine the type of reaction of the joint but that the localization of the primary infection was the determining factor. Sepsis developed in 7 of the 9 cases in which the acetabulum was injured.

Seven cases were classified as combination injuries and in 5 sepsis developed. Hampton reviewed 39 cases of gunshot wounds of the hip joint and found that when a single component of the joint was damaged, sepsis occurred in only 9 of 18 cases; when multiple components were damaged, sepsis occurred in 17 of the 21 cases.

Pelvic abscesses developed in 3 cases. Freiberg points out that the lymphatics draining the intracapsular structures of the hip joint converge to arteries within the pelvis.

Primary formal arthrotomy was performed in 12 of the 19 combat-incurred wounds. The other 7 combat-incurred wounds received initial superficial débridement of soft tissues. In 6 of the 7 cases sepsis developed; 3 of the patients required secondary incision and drainage of the hip joint. During World War II, 44 gunshot wounds of the hip in the British Army were reported by Ellis. Only 10 pa-

Fig. 5. Wound of femoral head resulting from small arms fire in 40 year old patient. Roentgenogram 12 years after injury; subsequent arthroplasty.

Fig. 7. Wound of upper acetabulum, femoral head, and femoral neck resulting from small arms fire in 25 year old patient. Roentgenogram 4 months after injury.

tients had a good range of motion of the involved joint, and all escaped infection. Final results were known in 16 septic cases, and ankylosis had resulted in 13 of the 16 patients. Urist reviewed 29 cases of hip joint wounds in 1947. Sepsis occurred in only 9 of the 29 cases, but only 9 of the patients had less than 25 per cent disability. As Churchill has indicated, during World War II the surgical management of hip joint wounds evolved from superficial débridement and observation to formal arthrotomy and extensive excision of devitalized tissues.

What still seems to be the optimum treatment for gunshot wounds of the hip was crystallized in the Army Technical Bulletin (10). That treatment can be outlined under the following principles: (1) operation at the earliest possible opportunity, (2) wide exposure of the joint, by means of formal arthrotomy, in order that the capsule and the inside of the joint can be thoroughly inspected, (3) the joint should be irrigated and completely cleansed of all devitalized bone, cartilage, and foreign debris, (4) the joint capsule should be closed "watertight" at all points, (5) antibiotics locally and systemically, (6) complete immobilization of the joint postoperatively, and (7) secondary closure of the wound on the fourth to seventh postoperative day.

SUMMARY

Gunshot wounds of the hip joint have the highest mortality and the greatest degree of shock of all joint wounds. The mortality of combat-incurred gunshot wounds of the hip has decreased since World War I and the prognosis of these injuries has definitely improved.

Twenty-four cases treated by the orthopedic staff at Brooke Army Hospital are presented. Seventeen of the cases were incurred during the present Korean conflict. Five of the wounds were not incurred in combat; 1 patient is a follow-up from World War I; and 1 patient was wounded during World War II. Nine patients have a good range of motion; 1 has had arthroplasty; 1 has painful, limited motion; and in 13 ankylosis has occurred. Twenty-two (91.6 per cent) of these patients have painless weight-bearing extremities.

Gunshot wounds of the hip joint involving multiple components of the joint or the acetabulum have a higher incidence of infection. The duration of sepsis has decreased with current surgical techniques and modern antibiotics.

The prognosis of the individual case can be estimated from the localization of joint involvement. Patients with involvement of the capsule only had a good range of motion in 75 per cent of cases. Patients with involvement of the superior margin of the acetabulum had upward migration averaging 3.0 centimeters and corresponding shortening of the involved extremity. All patients with involvement of the upper acetabulum progressed to ankylosis of the involved joint.

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THE GENERAL NATURE OF THE MOLECULAR ALTERATION OF COLLAGENOUS SUTURE IN VIVO

H. VINIK WEISS, Ph.D., VINTON E. SILER, M.D., F.A.C.S., and
ROBERT M. LOLLAR, Ph.D., Cincinnati, Ohio

THIS study has investigated the general nature of the molecular changes which provide for the solubilization of collagen in an in vivo system. With the exception of the investigation by Haugaard, Thoennes, and Hall, the results of which will be given subsequently, no attempt has been made to evaluate the fundamental processes which are involved in this transformation.

In the in vivo digestion of collagenous sutures, a period of lengthy duration is observed in which the protein is refractory to solubilization. This suggests that the collagen is undergoing a preliminary conditioning reaction which is requisite for enzymatic attack. This interpretation is in accord with the views expressed by Linderstrom-Lang (6, 7), in accounting for the accepted theory of enzyme action. Denaturation, a conditioning reaction (6), or the cleavage of a number of "strategically" important peptide bonds (7) is assumed to occur prior to the enzymatic hydrolysis of many proteins. Evidence of lateral bond rupture and/or the fission of small numbers of peptide bonds, in the stage preceding the onset of appreciable hydrolysis, should therefore be demonstrable in the in vivo digestion of collagenous suture. In 1946 Haugaard, Thoennes, and Hall demonstrated by measurements of hydrothermal stability that lateral bonds are ruptured progressively in the in vivo process.

No evidence of lateral bond rupture has been established to date. Furthermore, it appears likely that more than the rupture of secondary forces is involved in the preliminary stages of in vivo digestion. In this study corroborative evidence of these factors has been sought. For reasons which will be discussed later, profound changes in tensile strength prior to the period of solubilization cannot be entirely explained on the basis of loss of lateral cohesion, provided that the probable mechanism of rupture under stress is considered.

Meyer and Alfrey discuss a number of defined factors which influence the tensile strength characteristic of fibers. Fibers which are composed of long primary valence chains are characterized by high tensile strength, although the value obtained experimentally is usually considerably lower than that which is calculated from theory. This discrepancy may be accounted for by the fact that in practice, not all the chains within a fiber are put under stress simultaneously, and the force required for rupture is obviously influenced by the number of chains which bear the stress. Hence, the fibers in which the degree of orientation is high more nearly approach the tensile strength which is predicted from purely theoretical considerations.

In collagen the polypeptide chains are arranged more or less parallel with the fiber axis. Despite this alignment, it was found by Highberger that the theoretical tensile strength is 30 times greater than the observed tensile strength, if rupture of the weakest primary valence force in the chain (the C-N bond) is assumed. It was, therefore, concluded that the most probable mechanism of rupture in collagen consists of breaking the lateral cohesive forces. This type of cleavage permits one chain to slip over another and consequently to break.

Since in a mechanism of this nature, the cleavage of relatively few peptide bonds may have a pronounced influence on tensile strength, evidence for such cleavages has been sought. Also of interest is the qualitative

From the Surgical Chemistry Laboratory, Department of Surgery, College of Medicine and from the Department of Basic Science in Tanning Research, University of Cincinnati, Cincinnati, Ohio.

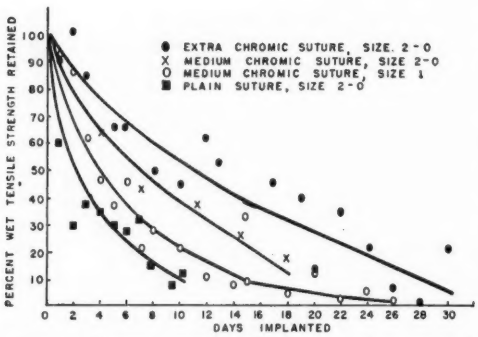
EXTRA CHROMIC SUTURE, SIZE 2-0
MEDIUM CHROMIC SUTURE, SIZE 2-0
MEDIUM CHROMIC SUTURE, SIZE 1
PLAIN SUTURE, SIZE 2-0
PERCENT WET TENSILE STRENGTH RETAINED
DAYS IMPLANTED

Fig. 1. Change in wet tensile strength of 4 types of suture in in vivo digestion.

appraisal of the contribution of reduction in lateral cohesion to the loss of tensile strength.

EXPERIMENTAL METHOD

Implantation studies were conducted with a variety of sutures. This was for the purpose of evaluating the general pattern of the changes, with regard to solubilization and tensile strength which sutures undergo during digestion time. The following types of sutures were studied: (1) plain, size 00; (2) medium chromic, size 00; (3) medium chromic, size 1; (4) extra chromic, size 00. (Size 00 and size 1 sutures have approximate diameters of 0.35 mm. and 0.65 mm., respectively. The chrome content of the medium chromic sutures is about 0.4 per cent and that of extra chromic about 0.55 per cent.)

Implantations were performed on white male rabbits, the weights of which ranged between 5 and 10 pounds. The operative procedure was carried out under strict aseptic conditions.

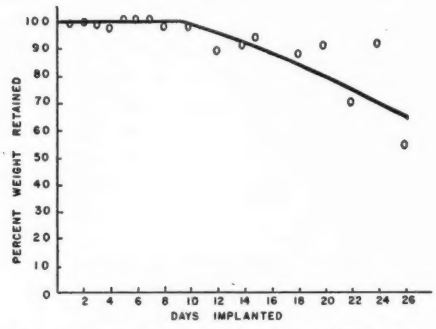

Fig. 2. Change in weight of medium chromic sutures, size 1 in in vivo digestion.

The implantation technique comprised drawing a 7 inch stilet threaded with the suture through 2 incisions, 4 inches apart. The knot binding the suture to the stilet was cut on the side proximal to the incision, and the stilet was withdrawn. All implants were embedded in the subcutaneous tissue. Six portions of the same suture were introduced into each rabbit. The remainder of each strand was reserved for control analyses. At predetermined intervals, the animals were sacrificed and the 6 implanted sutures removed.

Each implant was subjected to tensile testing under wet conditions, and either weight or nitrogen determinations were made.

In a subsequent phase of the investigation, the extent of peptide bond hydrolysis was determined in the in vivo process prior to solubilization. Since large quantities of implant were desired for these analyses, the implantation procedure was modified. This modification generally involved making 2 transverse incisions about 4 inches apart. The suture was threaded through the subcutaneous layer by passing the stilet to which it was attached through 1 incision and out of the other. The path was retraced in the opposite direction when the free end or loop of the suture approximated the line of the incision. In this manner, it was possible to implant 2 sutures (about 100 inches) into a rabbit.

ANALYTIC PROCEDURES

A Scott IP-4 serigraph was used in the tensile strength determinations. The sample was secured between the jaws of a stationary clamp and a movable clamp, the latter being attached to a carriage. The carriage rested on rails, the plane of which changed at a constant rate when the instrument was in operation. The instrument was so designed that the full load of the carriage was transferred to the sample 20 seconds after the initiation of incline. A mechanism was also provided for automatically recording on a chart the point at which rupture occurred. The breaking strength was calculated from the known load on the carriage.

In order to characterize the contribution of reduction in lateral cohesion to the loss of tensile strength, a portion of implant was tested under wet conditions and compared with another segment of the same implant, which was shrunk at 70 or 100 degrees C. For this purpose, 2 sutures were implanted into each of 14 rabbits. To afford closer observation of events, the digestion process was impeded by implanting the suture within a relatively confined area. The sutures used were medium chromic, size 1. The animals were sacrificed at various intervals over a period of 17 days, to obtain a wide range of residual tensile strength values. Upon removal of the implants, 3 segments of each were cut of sufficient length to allow for at least 4 replicate analyses. The segments were prepared for dry, shrunken, and wet testing. Dry conditioning comprised air-drying at about 70 degrees C. for 48 hours. The shrunken samples were obtained by subjecting previously soaked implants in water maintained at 70 degrees C. for 45 seconds, or in boiling water for 30 seconds. The tensile strength was recorded in pounds.

Solubilization was determined either by weight or nitrogen analysis of a known length of implant. Frequently, on removing implants from an animal, a mucoid-like deposit was observed to surround the suture. This deposit was carefully removed prior to analysis. The portion of implants used for either of these analyses was that which had been previously subjected to tensile testing.

Nitrogen was determined by the standard micro-Kjeldahl procedure. Where weighings were substituted for nitrogen determinations, the measured length of suture was air-dried for 48 hours. The sample was weighed to 0.01 milligram on a microbalance and results were expressed as milligrams per inch of suture.

For the purpose of determining the extent of peptide bond hydrolysis at a stage of the digestion process prior to solubilization, amino nitrogen analyses were performed. The method adopted for this analysis was the Van Slyke procedure, as modified by Doherty and Ogg for application to insoluble proteins. The results were expressed as per cent amino nitrogen per gram moisture free protein.

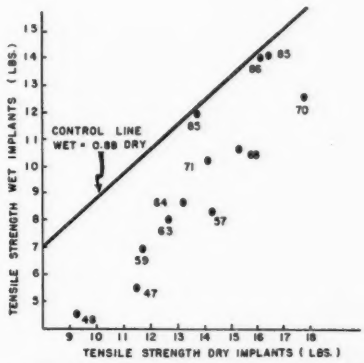

Fig. 3. Tensile strength during the course of digestion of wet and dry conditioned implants showing wet/dry ratio (per cent) at each experimental point and deviation from average control line.

RESULTS

Figure 1 shows the relationship between digestion time and the per cent of tensile strength retained for the 4 types of sutures which were studied in the preliminary phase of this project. Each point represents an average of the tensile strength retained for implants (usually 6 in number) which were removed at the designated intervals. The essential feature to be noted is that a marked decrease in tensile strength occurs in the early stage of digestion. Following this period the change is more gradual.

Figure 2 shows the relationship of solubilization and digestion time for medium chromic suture, size 1. In the first 10 to 12 days of implantation the suture is refractory to solubilization. Following this period a gradual loss in weight is manifested. On the twenty-sixth day about 50 per cent of the implant is solubilized. The general characteristics of the solubilization curve are essentially the same for the other types of suture investigated, whether examined by weight or nitrogen analyses.

Figure 3 shows the relationship between the wet and the dry strength of the removed implants. The mean value of the ratio of the wet to dry strength on the original control sutures was 0.88, which is shown as the diagonal line in Figure 3. It is shown that as the implantation weakens the sutures, they fall further and further below the control line.

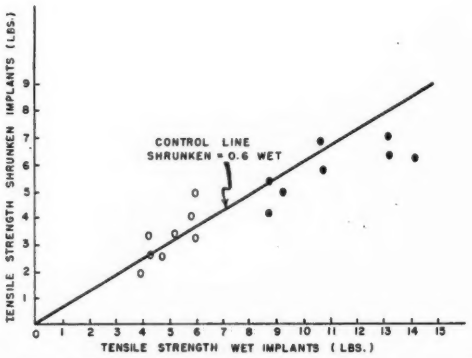

Fig. 4. Tensile strength relation during the course of digestion of wet and shrunken (100 degrees C., 30 seconds) implants, and average control line.

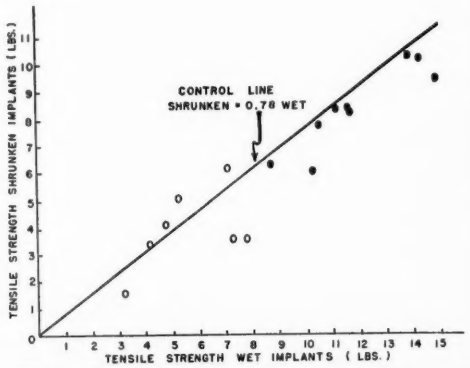

Fig. 5. Tensile strength relation during the course of digestion of wet and shrunken (70 degrees C., 45 seconds) implants, and average control line.

Figure 4 presents the relationship of the wet strength of the original implants to the strength of the shrunken implants. The diagonal solid line illustrates that the control sutures showed an average shrunken strength which was 0.6 of the unshrunken strength. The data were secured on sutures shrunken for 30 seconds at 100 degrees C. Figure 5 shows similar data for sutures shrunken at 70 degrees C. for 45 seconds, with 78 per cent of the strength retained after shrinking. The sutures shrunken at 70 degrees C. retained 65 per cent of their original length, whereas at 100 degrees C. they retained 58 per cent of their original length.

The data secured on the amino nitrogen values of the original control sutures and the implanted sutures after 8 and 20 days indicate that there is no detectable difference between the implanted sutures and the control sutures, when the error of the procedure is considered.

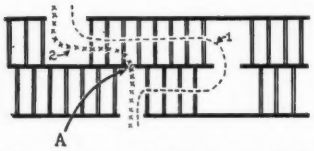

Fig. 6. The mechanism of slipping and the influence of peptide bond fission. The horizontal lines represent polypeptide chains and secondary valence forces, respectively. In the intact fiber the course of rupture follows path *1*. By virtue of peptide bond cleavage at *A* the path is altered and proceeds by way of *2*.

DISCUSSION

These data indicate that when compared to the original sutures, collagenous sutures implanted in rabbits show, upon removal after several days of implantation, the following characteristics: (1) no detectable increase in the free amino nitrogen obtained by the Doherty and Ogg method; (2) an early rapid loss in strength of the suture, followed by a slower rate of strength loss as the implantation time increases (Fig. 1); (3) an inhibition to weight loss in the earlier stages of implantation, followed by an accelerated weight loss phase (Fig. 2); (4) the wet strength to dry strength ratio of the implanted sutures falls more rapidly as the strength loss increases (Fig. 3); (5) the ratio of the wet strength of the original implants to the wet strength of the shrunken implants is less than the ratio for the control sutures in the early stages of strength loss, but this difference is minimized as the implants lose wet strength (Figs. 4 and 5); (6) (a) progressive depression of the shrinkage temperature during implantation, which confirms the observations of Haugaard, Thoennes, and Hall, (b) a loss of chrome, which however is not complete as long as suture pieces can be recovered. (This unremoved chrome may not possess any tanning function; this is suggested by the low shrinkage temperature of the implants, which is less than that for the control of unchromicized sutures in many cases.)

Two possible mechanisms may logically play a role in these phenomena. First, the lateral bond cohesion of the sutures may be decreased. Secondly, peptide bond rupture may weaken the protein. We believe that these data indicate that both mechanisms are involved.

Highberger notes that the hydrothermal stability of collagen has been taken as evidence for the increase in the lateral cohesion of collagen as a result of tannage. Further, he states that in the presence of strong lateral cohesion or cross-linking, collagen should show high strength. Thus, Jacobson and Lollar have shown that mercuric acetate, a protein bridging agent, does increase the wet strength of collagen. On the other hand, this work shows that both the shrinkage temperature and the wet strength of the sutures is decreased. Therefore, it is logical to assume that these changes do reflect a decreased lateral cohesion of the collagen due to detannage and the resultant swelling of the wet implant.

This weakening of the lateral cohesion of the implant did not, however, proceed to the point of spontaneous shrinkage. On removal the implants were the same length as the original ones, as long as intact implants could be secured. Yet, the wet strength of removed implants was considerably less than that of the sutures shrunken in hot water. Thus, the original sutures lost only 40 per cent of their wet strength when shrunk at 100 degrees C. (Fig. 4), and sustained only 22 per cent loss during shrinkage at 70 degrees C. (Fig. 5). On the other hand, the implanted sutures lost at least three-quarters of the strength very quickly (Fig. 1). Since the disorientation during shrinkage proceeded further than that during implantation, some additional mechanism must be involved. This we believe to be peptide bond rupture.

It is shown that the shrunken implants removed early in the implantation period, when their wet strength was still high were weaker than the shrunken control sutures. These data are represented by the filled circles in Figures 4 and 5. On the other hand, the open circles for data secured on the very weak implants fall around the line for the shrunken controls. This seems indicative of an early rupture of a few peptide bonds, followed by a period during which decrease of the lateral cohesion and solution of the protein takes place. Early rupture of the peptide bonds is also consistent with the solubilization data in Figure 2.

The data on the numbers of free amino groups in the collagen during implantation were secured in an attempt to show this peptide bond rupture. The errors of the procedure are so large that we could not detect less than one peptide bond rupture in 225 residues, which may be far more than are required in view of the possible molecular size of collagen.

The influence of peptide bond cleavage on tensile strength is demonstrated diagrammatically in Figure 6. The horizontal and double vertical lines represent polypeptide chains and secondary valence bonds, respectively. The path of rupture is indicated in Figure 6 shown by the numeral *1* in the intact fiber. For rupture to occur in this hypothetical case, twelve lateral units are required to break. If on the other hand, a peptide bond is cleaved at position *A* (Fig. 6) the number of lateral bonds which must rupture is reduced by 75 per cent, since slipping has the natural tendency to follow the path of least resistance, as represented by the numeral *2* (Fig. 6). It is realized that cleavage in the position shown is ideal; clearly, however, cleavage in even less favorable positions significantly influences the tensile characteristics.

CONCLUSIONS

Implantation of collagenous sutures results in a detannage shown by lowered shrinkage temperature, a delayed solubilization and a rapid loss of strength. These data seem consistent with the interpretation that an early rupture of a few strategically located peptide bonds is followed by a decreased lateral stability of the collagen, which results in the complete dissolution of the suture.

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EDITORIALS

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FEBRUARY, 1954

THE NEED FOR ABLE PROFESSIONAL LEADERSHIP IN SMALL COMMUNITIES

MEDICINE at the grass roots is destined to undergo tremendous changes in the years ahead. Never has the county medical society been presented with such opportunity nor with so much responsibility. Good medicine is moving to the country. If leaders in local societies are able to read the signs of the times and act with vision, the results will be little less than revolutionary.

To plan medical care for an entire state which includes industrial and rural populations is an almost impossible task, but to survey and organize the medical care for the people of a single county is within the realm of possibility and something that can and should be done. The group that can do it are the doctors serving the area.

The place to start is with the local hospital. Modern medicine revolves around an adequate workshop, and elimination of friction in its operation is the first prerequisite. The commonest cause of friction is local jealousy. Doctors are prone to the fallacious belief that acquiring a competitor will lead to financial ruin. Experience proves this to be untrue for invariably both persons are soon as busy as they can be: business is not divided but multiplied. One is reluctant to bring up the sin of professional jealousy for review, but every doctor knows how much we worship the green-eyed goddess and how she has led us all astray. Furthermore, our petty attitude toward one another is a source of embarrassment to the laity and drives patients away from home where they do not have to worry about hurting someone's feelings.

The basis for bringing modern medicine to the crossroads must be deliberate and friendly co-operation among the physicians. The younger men who have been trained in large centers where they are used to working with other residents do not seem to be so jealous of each other. However, when they attempt to enter practice and are kept off the hospital staff by a clique and when every possible obstacle is placed in their way by fearsomely shortsighted older physicians, they soon learn to retaliate in kind and the fat is in the fire. The public will little longer continue to be amused by such childish behavior.

The revolution in medicine at the county level is being perpetrated by the recent graduates who have had training in the specialties and who are drifting away from the large cities. The people want them and flock to their offices when and where they are available. As it becomes common knowledge that a real specialty practice may be developed away from the din and congestion of the cities,

the present trickle will become a flood. A pediatrician will need, demand, and finally obtain a children's ward in the local hospital where therapy can be adequately administered. The obstetrician will improve his department in a similar way. A well trained internist must insist upon a laboratory service that is as complete and accurate as possible. After much trial, error, and many difficulties these things will become working realities.

The toughest nut to crack is general surgery. For one reason or another a great many doctors want to do a "little surgery." It seems to be the hallmark of medical pride. Incidentally, the doctors who do a "little surgery" are often the most jealous mortals on the face of the earth and they make most difficulties for the beginning surgeon who tries to set up shop. But sooner or later a doctor with adequate surgical training locates, limits his practice to general surgery, and sticks it out. He really has to be good but if he has mettle, a lot of patience, and is given time, no general practitioner can compete with him in his surgical field. In the end, if he is honest and tactful, he will become a tremendous asset to the community, a tower of strength to his associates, and will help to save many lives.

The establishment of a competent hospital in association with appropriate medical skills is the start of the race. Once done, the medical community must broaden its horizons. Now is the time for the local medical society to take the large view and as a group look at the overall health picture in the entire area. Survey the field: certain groups will be found to be receiving inadequate care; public health measures will be found to be insufficient; economic aid will be needed by many and must be provided; the medical library will be found to be deficient or absent altogether.

A hospital will be no more than a name which does not become a teaching hospital in so far as this is possible. Nurses should train nurses aides. The dietitian should interest high school girls and obtain their aid in making up attractive trays and spreading cheer in passing them. The laboratory should be training technicians to do routine work and encourage them to complete their training in larger centers.

The medical staff should now plan to provide preceptor training to a few medical students in connection with their medical education. Contact with a medical school will be stimulating and rewarding, and the individual physician will develop a new interest in medicine as he begins to participate in the field of education.

Eventually psychiatry will come to the country. At present a diagnosis of neurosis is about as popular as a diagnosis of syphilis was a generation ago. But every practitioner sees dozens of patients whose troubles are functional, and about all he can do for them is to try to be their friend and keep them away from the fellow who does a "little surgery." Sooner or later, some hardy souls with a missionary bent will come to the county seat towns to provide individuals and the community with some insight into the problems of mental illness.

Truly, disease prevention, accurate diagnosis, and effective therapy are actually possible for each and every community. The problem is one of the great frontiers of modern medicine. Vision, leadership, and co-operation by the medical profession at the county level can make this one time dream a present day reality.

GEORGE A. COLLETT.

FINGERPRINT EDEMA

FINGERPRINT edema, generally thought to be indicative of intracellular fluid excess, is one of the more controversial clinical signs. It is frequently positive during very hot weather, in critically

ill patients, and in the lower extremities after long periods of erect posture. The test is positive when the whorls of the fingerprint are clearly visible after circumferential manipulation of a pressure point on the forehead or sternum. It is to be distinguished from pitting edema, a sign of extracellular fluid excess.

The differential diagnosis of excess or deficit of intracellular fluid is difficult on clinical grounds alone because of identity of neurologic signs in the early phases of both types of imbalance. Were fingerprint edema a valid sign, it would have considerable usefulness. It becomes important, therefore, to examine its significance.

Only the most casual reflection is sufficient to question the ability of the half-dead cells of the skin to serve as reliable indicators of fundamental intracellular changes. Especially is this true in the light of recent evidence that tissue metabolism may be of paramount importance in determining the exchange of water between the extracellular and intracellular spaces. The histologists have long recognized the predominant collagen structure of skin, a fact well known in the leather industry.

A recent review of the literature of the leather chemists records that a "collagen fibril is essentially a long thin, single 'crystal'; as such, its formation or dispersion, synthesis or degradation, is expected to be largely at the mercy of its surroundings."[1] Changes in physical structure are necessarily determined by environmental alterations. It is but a small hurdle to assume that fingerprint edema is due to increased uptake of extracellular fluid by collagen in consequence of alterations of the interstitial fluid.

There is great need to identify some reservoir other than the intracellular compartment to contain the flood of extracellular fluid, suggested by numerous observations on the variable size of the sodium, chloride, and thiocyanate spaces, and unassociated with confirmatory clinical signs of comparable excess of intracellular fluid. Our studies encourage us to believe that a positive fingerprint edema test is indicative of the existence of such a reservoir. If it can be demonstrated that collagen accumulates water and sodium to buffer intracellular fluid changes, it would do much to clarify paradoxical alterations of fluid equilibrium currently assigned to altered cellular activity due either to drugs or to disease.

Aside from these hypothetical considerations, a positive fingerprint edema sign should indicate water excess within the body. Usually, both water and sodium should be restricted until renal excretion has restored osmolar equilibrium and fluid volumes, and the fingerprint edema has disappeared. We believe the sign has considerable utility in routine postoperative management and is as valuable as the flame photometer in the handling of burned patients.

CHAMP LYONS.

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THE SURGEON AT WORK

THE USE OF BENZOCAINE FOR TOPICAL ANESTHESIA IN CYSTOSCOPY

J. E. BYRNE, M.D., St. Louis, Missouri

URETHRAL instrumentation, and in particular cystoscopy, has long been an unpleasant procedure for many patients. In these times of extensive diagnostic evaluation seldom is the patient seen that is not conversant with the trials of cystoscopy. A great share of the blame for this unsavory reputation can be laid to the inadequacy of the local anesthetic agents in common use.

It is readily apparent that only a general anesthetic agent is capable of relieving all of the discomfort attendant to urethral instrumentation. The risk of a general anesthetic more than outweighs the advantages in the performance of minor operative procedures. Consequently a variety of topical anesthetic agents have been offered to fill this gap in our anesthetic armamentarium. The chief objection to topical anesthetic agents in common use has been their inability to produce sufficient urethral anesthesia for the desired instrumentation. Cocaine either in a solid form or in a variety of aqueous solutions was probably the first and most effective agent used in urethral anesthesia. The drug fell into disrepute following a wave of communications on the dangers attending its use. More recent investigations have shown that most instances of untoward result following the use of cocaine could be blamed on the improper use or preparation of the various forms. The anesthetic qualities of the drug are seldom questioned, and it remains today the standard of topical anesthetic activity.

The ideal topical anesthetic agent for use in the urethra would of necessity fulfill the following qualifications: (1) It must be of prompt and reasonably intense action in anesthetic effect. (2) It must be of low toxicity. (3) It must be readily stored in a usable solution. (4) It must be highly miscible with water to a degree that it will not interfere with cystoscopic vision. (5) It must be capable of being prepared as a sterile solution.

From the Department of Urology, St. Louis University School of Medicine, St. Louis, Missouri.

Tainter has shown that benzocaine (ethyl aminobenzoate) is an excellent topical anesthetic agent when concentration of at least 10 per cent can be obtained. The low solubility of the substance has prevented the prior use of this drug in concentrations greater than 2 or 3 per cent (solubility 1.0 gm. per 2,500 c.c. of water). The relatively low toxicity of benzocaine was shown by Adraini who used cocaine as the standard with a toxicity index of 1 and found the relative toxicity of benzocaine solutions to be 0.1.

The substance used in this study was a 10 per cent solution of benzocaine dissolved in a series of carbowaxes to increase the solubility of the benzocaine. Oxyquinoline benzoate was added to the solution for its bacteriostatic effect. The solution is water miscible and has a soapy consistency that flows readily over the tissues. Previous studies using a 20 per cent ointment of the same preparation have shown its efficacy along with low toxicity in other areas requiring topical anesthesia.

METHOD

The 10 per cent solution of benzocaine was used as the sole urethral anesthetic agent in 500 cases. Only those cases with recent or active urethral bleeding were excluded from the study. The majority of the observations are based on the results obtained in cystoscopy. For purposes of standardization, the instruments used in all of the cases were either the F-24 Brown-Burger cystoscope, or the F-22 McCarthy panendoscope. Frequently it was necessary to dilate the urethra with a series of steel sounds prior to the passage of the cystoscope or the panendoscope. The patients were all done on an outpatient basis without the benefit of premedication prior to instrumentation.

In the male patient 15 cubic centimeters of the 10 per cent benzocaine solution was injected directly into the urethra with a blunt tip urethral syringe. Sufficient pressure was exerted to be sure that the head of the injected column of anesthetic agent entered the bladder. In the female patient,

the anesthetic agent was first supplied to the urethral meatus with a cotton applicator dipped into the solution; 5 cubic centimeters of the solution was then injected directly into the urethra with a pointed bulb syringe. After a waiting period of from 2 to 3 minutes, the urethral instrumentation was carried out. The lubricating action of the anesthetic agent was not sufficient for the ready passage of the instrument and was supplemented with a water soluble lubricant.

RESULTS

The results were satisfactory in 225 of 300 males and in 90 of 100 females. Insufficient anesthesia was noted in 75 males and in 10 females. Satisfactory urethral anesthesia was obtained in over 75 per cent of all the cases; the greatest incidence of failure was noted in the male patients. All of the patients complained of a mild and transient urethral sensation following the introduction of the anesthetic agent; in none of the cases was it necessary to delay or postpone the urethral instrumentation because of the local response. This action has been attributed to the hygroscopic nature of the benzocaine solution.

Cystoscopic vision was impaired only at the beginning of the observation, as soon as the irrigating solution began to enter the bladder, the anesthetic solution lying on the floor of the bladder was readily dispersed with the irrigant. There was no detectable interference with the bacteriologic studies on the urine obtained at the time of cystoscopy. In vitro studies on the inhibitory action of the 10 per cent benzocaine solution on Escherichia coli organisms revealed a minimal bacteriostatic action with the dilutions estimated to be that of the amount of the drug present in the bladder at the time that the urine was taken for routine culture. In none of the cases was evidence of a local or systemic response noted. All of the patients were seen subsequent to the use of the drug, and approximately 15 per cent of the male patients stated that they had experienced burning on urination for a period varying from 24 to 36 hours following the examination. We attributed little significance to this response in so much as it is a frequent accompaniment to cystoscopy with or without a local anesthetic agent.

CONCLUSIONS

A 10 per cent solution of benzocaine dissolved in a series of carbowaxes has, in our hands, been both a safe and effective agent in the topical anesthesia of the urethra prior to urethral instrumentation.

REFERENCES

1. Adraini, J. The Pharmacology of Anesthetic Drugs. P. 49. Springfield, Ill.: Charles C Thomas, 1941.
2. Tainter, J. L. The composition of local anesthetic solutions. Anesthesiology, 1941, 2: 489–502.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE monograph entitled *The Practice of Balanced Anesthesia*[1] reports the author's experience in the use of a prescribed mixture of anesthetic drugs as the general anesthesia of choice in the majority of operations. The described technique utilizes a barbiturate induction upon which is superimposed a mixture of approximately 45 per cent nitrous oxide, 10 per cent cyclopropane and 45 per cent oxygen administered in a semiclosed, carbon dioxide absorption system. The first section of the book deals with the application of the technique to various types of operation. Part II discusses the use of spinal analgesia with the advocated mixture of anesthetic drugs. A section is devoted to special problems including the use of the mixture for small animal surgery. The longest part of the book is a historical essay on the evolution of balanced anesthesia.

The merit of the publication is debatable. The premise that a prescribed mixture of drugs is suitable for all situations is quickly refuted by the account itself. Moreover, the concept is a fallacy, a distortion of the import of "balanced anesthesia" as propounded by Lundy in 1926. This is particularly evident in the essay in which the groping efforts of the early workers are interpreted as a search for balanced anesthesia. Some general information which may be of interest to the student is included, but it is available in more objective form in other publications.

MARY F. POE.

THE author of *Die Wirbelsaenlentuberkulose und ihre Differentialdiagnose*[2] is primarily a roentgenologist but has been interested in the study of tuberculosis of the spine for many years and has done investigative work to establish methods of early and accurate diagnosis of the disease. Most of the material is from his own private practice, but some of the illustrations are reproductions of roentgenograms by colleagues in other countries.

This volume is a monograph written with the purpose of demonstrating modern methods for the diagnosis of tuberculosis. Forty examples of different stages of tuberculosis are cited giving a telegraphic description in each case and demonstrating the lesions with excellent roentgenograms. With the planogram technique he can frequently demonstrate the bone destruction and soft tissue involvement better than with the routine technique.

The book contains a complete differential diagnosis including all nontubercular spondylitis. He shows the early and late stages of ankylosing spondylitis. There is a thorough discussion of Scheuermann's disease showing three stages of development. Each stage is demonstrated by excellent roentgenograms. He shows two cases in which the vertebrae have become confluent, probably secondary to a healing process in Scheuermann's disease. Several cases are shown in which there is a separation of the margins bringing about a loose fragment. Sometimes this occurs at the anterior margin and sometimes at the posterior margin. He gives a small series of vertebra plana (Calve) in which there is a compression and condensation of the vertebra. Then he describes a whole series of defective vertebra—congenital anomalies—with illustration by roentgenograms.

He gives some excellent examples of osteoporosis, osteomalacia, and osteitis fibrosa cystica. There is also a chapter on bone tumors as they occur in the spine.

The monograph is concerned with the development of tuberculosis as it occurs in the spine and to a lesser degree in the methods of treatment. The author believes that the infection occurs early, that it is widespread, that there may be many patent foci and that these foci can flare up at a later date as a result of local trauma or lowered resistance.

The large number of well chosen roentgenograms are excellent and in each case demonstrate the lesion the author describes. It is an unusually complete monograph and I recommend it to all roentgenologists, orthopedic surgeons, and to whoever is concerned with the differential diagnosis of tuberculosis of the spine.

EMIL D. W. HAUSER.

IN THE third edition of *Human Neuroanatomy*[3] by Oliver S. Strong and Adolph Elwyn the authors have maintained the clear, concise manner of exposition and the careful correlation of anatomic data with physiologic and clinical material which was so

[1] THE PRACTICE OF BALANCED ANESTHESIA. By Sylvan M. Shane, D.D.S. Preface by Juan White Morquecho, M.D. 186 pages, with 12 illustrations. $5.75. Baltimore: Lowry & Volz, 1953.

[2] ARCHIV UND ATLAS; DER NORMALEN UND PATHOLOGISCHEN ANATOMIE IN TYPISCHEN ROENTGENBILDERN. DIE WIRBELSAEULENTUBERKULOSE UND IHRE DIFFERENTIALDIAGNOSE. By Priv.-Doz. Dr. J. E. W. Brocher. 272 pages, with 172 illustrations. DM 78. Stuttgart: Georg Thieme Verlag, 1953.

[3] HUMAN NEUROANATOMY. By Oliver S. Strong and Adolph Elwyn. 3rd ed. 481 pages, with 357 illustrations. $7.50. Baltimore: The Williams & Wilkins Co., 1953.

outstanding in the earlier editions. The present revision of the book has brought it up to date by the addition of recent developments in neurophysiology as well as by augmenting the text and illustrative material on certain sections of the neuroanatomy.

The plan of presentation follows the generally accepted principle of starting at the periphery of the nervous system and working upward to the suprasegmental levels. The gross structure and relationships of each region are reviewed following which the more intimate anatomy is presented with the aid of accompanying photomicrographs and diagrams. These are helpfully interspersed with the text so as to enable the reader to follow the discussion without the necessity of referring to an atlas at the back of the book for the illustrative material. The functional systems included in each region are reviewed at the end of the appropriate section with a discussion of their physiologic and clinical significance. This provides the reader with additional information and interest which greatly facilitates learning and retention of the material presented.

In addition to the use of material from current investigations throughout the discussions and references, several sections of the book have been considerably revised and expanded. The chapter on the neuron has been enlarged to contain an excellent discussion of the histologic changes associated with degeneration and regeneration. In the section of the mesencephalon, the reticular formation has been presented in more detail with especial emphasis on the recent work by Magoun and Jasper in regard to its neurophysiologic significance. The anatomy of the thalamus and its associated pathways has been discussed in more detail and more fully illustrated. Material obtained from recent clinical and physiologic investigations has been incorporated into the section on the cerebral cortex with a discussion on the general nature of cortical functioning. At the end of the book there is an excellent bibliography which contains references to the more important recent contributions to the anatomy and physiology of the nervous system.

Because of its constant emphasis on the functional significance of the anatomic structure of the nervous system, this book is highly recommended to those who wish to gain a practical working knowledge of human neuroanatomy. To the clinician and medical student alike this work will serve as a clear and interesting exposition of the essentials of neuroanatomy as well as a convenient and timely reference source.

FRED D. FOWLER.

THE authors of *Slipped Capital Femoral Epiphysis*[1] have collected and presented an excellent group of well reproduced roentgenograms which illustrate the yearly changes in appearance of the developing normal proximal femur. This series of x-ray films is supplemented by many examples of the several types and stages of slipped capital femoral epiphysis, both treated and untreated cases.

Documenting the x-ray appearance at the normal and pathologic hip joint in this manner facilitates study of this particular lesion, but their abundant illustrations are more likely to be useful to the practicing orthopedic surgeon and radiologist as a reference in the study of normal hip joint development than as a book on the slipped capital femoral epiphysis.

In addition to this unusual x-ray series they have included a summary of their analysis of 68 patients with slipped capital femoral epiphysis treated at the Massachusetts General Hospital. From the information obtained from these cases, in which there were 81 instances of this type of pathologic condition, the authors have derived several policies regarding management which will interest all who encounter this challenging problem in practice.

Several of their recommendations in the controversial aspects of management will undoubtedly provoke discussion among those interested in this subject, particularly in regard to open reduction and nailing and time of beginning weight bearing. A later follow-up of cases treated by their chosen methods should be interesting, such as the number who later required arthroplasty or fusion.

The book contains an excellent collection of x-ray films of the developing hip joint and incidentally an article reviewing some aspects of a group of cases treated at one hospital.

FRANK E. STINCHFIELD.

WITH characteristic German thoroughness Dr. Max Grob[2] of the University Children's Clinic at Zurich, Switzerland, has recently produced a splendid monograph on the anomalies of the alimentary tract resulting from abnormalities of the fetal intestinal rotation. The material is based on 28 clinical cases, in 13 of which the observations were made at operation, and in 15 the studies were made at autopsy.

In his introduction the author brings out the fact that in the early years reliable information on this subject was derived principally from anatomic studies, whereas since the roentgen era observations from x-ray films and the fluoroscope have enormously added to our ability to understand and clarify these intricate problems.

After a brief review of the normal development of the alimentary tract in the embryo the author discusses in great detail every conceivable type of abnormality of intestinal rotation, as it affects (1) the midgut (Nabelschleife) and (2) the stomach and duodenum (gastroduodenal Schleife) and throughout this discussion he emphasizes the all important point that one must take into account not only the

[1] SLIPPED CAPITAL FEMORAL EPIPHYSIS. Publication No. 153, American Lecture Series. A Monograph in American Lectures in Roentgen Diagnosis. By Armin Klein, M.D., Robert J. Joplin, M.D., John A. Reidy, M.D., and Joseph Hanelin, M.D. Edited by Aubrey O. Hampton, M.D. 130 pages, 77 illustrations. $6.75. Springfield, Ill.: Charles C Thomas, 1953.

[2] UEBER LAGEANOMALIEN DES MAGENDARMTRACTUS INFOLGE STOERUNGEN DER FETALEN DARMDREHUNG. By Max Grob. 148 pages, with 110 illustrations. Geb. Fr. 24. Basel: Benno Schwabe & Co., 1953.

primary pathology as it exists in embryonic life but also the secondary pathology which is superimposed during the days, weeks, months, or years after birth.

The 28 clinical cases are then presented in great detail, giving the essential history, physical findings, observations at operation or autopsy, and the clinical progress of those patients who survived. The text is well illustrated by many simple black and white diagrams, x-ray films, and actual photographs. There follows a brief discussion of symptomatology, in which the author records the frequency of other concomitant embryologic defects, therapy, and finally a summary in which the essential points in the monograph are emphasized.

To my mind this is a valuable contribution to the literature dealing with congenital developmental anomalies, because every phase of the problem is presented in much greater detail than one can find in any textbook on children's surgery. The author says in his preface that the clinical evidence of abnormalities of bowel rotation usually begin early in life and, therefore, they attract particularly the attention of the pediatrician and the surgeon who specializes in children, and I am inclined to agree with him in this statement. EDWIN M. MILLER.

THE four hundred page volume *Injuries of the Spinal Cord*[1] is a concise, modest but effective, discussion of experience-tested methods for the total care of the patient with injury of the spinal cord. Though it is a compilation of the ideas of nine different authors, each with his own special interest in such patients, yet the text is as closely integrated and smooth as if it were written by one author. The book is well bound, printed in excellent type that is easy to read, well illustrated, and has a comprehensive index and an excellent set of references at the end of each of the nine chapters. All authors represented drew their experience from their service in the Armed Forces during World War II, as well as from civilian practice.

The subjects covered are: neurosurgical aspects, urologic aspects, problem of nutrition, associated injuries and complications, treatment of decubitus ulcers, general program of rehabilitation, orthopedic principles as applied to the program of rehabilitation, and psychologic considerations. The discussion of the neurosurgical problems in the cord injured patient has been very well done, and while in some details some neurosurgeons may not agree with the author, there can be little argument with his general principles of care. This chapter alone would make good required reading for all young, and some older, surgeons, because of its direct, uncomplicated, and easy-to-understand contents. The section on the urologic aspects of the patient occupies approximately two-fifths of the entire contents of the book, which might be considered somewhat disproportionate, granting that the urologic care of the patient is of major and continuous importance throughout the remainder of the patient's life. It is excellent reading, but more detailed than necessary for the needs of a book of this nature. The section on nutrition is particularly to be commended for the excellent directions for the actual feeding problems which are always a part of the cord-injured program.

This common-sense, practical book is a direct expression of the reasons why the cord injured patient treated during World War II did so much better in every respect that was ever true at any time previously, and why the optimistic and courageous approach to the problem continues, through the Korean War and the results of many civilian accidents of every day, to produce ever better life and hope for these most tragically of injured patients.

JOHN MARTIN.

THE second volume of the first American edition of the renowned German text *Roentgen-Diagnostics*[2] completes the presentation of the skeletal system. The acclaim with which the first volume was received will undoubtedly be duplicated or surpassed by the second. All praise is due James T. Case for his fine editorship and his meticulous translation.

This volume is larger than the first by about 263 pages of text and 59 pages of triple column index, the latter for both volumes. Attention is called especially to the last two chapters. The first, "Differential Diagnosis of Skeletal Disease," includes skeletal charts showing the favorite localization of the more important bone diseases and then, in synoptic form, individual syndromes and diseases with their localization, symptoms, histology, and chemistry are listed. The last chapter presents skeletal diseases grouped by regions. There are 27 large charts with multiple drawings sketched from roentgenograms showing different lesions involving a specific region such as elbow, wrist, and spine. A short descriptive text accompanies each chart.

It is impossible to single out any of the formal descriptive chapters for special mention because of their excellence; all are very well written with details which are rarely found even in monographs. The illustrations which include roentgenograms shown in fluoroscopic rather than the usual roentgenographic image seen in most American texts, line drawings, photographs, and photomicrographs are practically countless. The excellence of these prints must be seen to be fully appreciated.

This Volume includes chapters on: bone tumors, skeletal malformations, the relation of vitamins and hormones to bone disease, joint surgery, the vertebral column, the skull and its contents (highly recommended), soft tissue roentgenography, and foreign bodies and their localization.

[1]INJURIES OF THE SPINAL CORD. Edited by George C. Prather, M.D., F.A.C.S., and Frank H. Mayfield, M.D., F.A.C.S. 396 pages, 125 illustrations. $8.75. Springfield, Ill.: Charles C Thomas, 1953.

[2]ROENTGEN-DIAGNOSTICS. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. 1st American ed., based on 5th German ed. English translation arranged and edited by James T. Case, M.D., D.M.R.E.(Camb.) Vol. 2. $45.00. New York: Grune & Stratton, 1952.

The editors of the German text which incidentally Dr. Case states has been closely adhered to were assisted by additional contributions from Dr. E. Brandenberger, Dr. A. Brunner, Dr. U. Cocchi, Dr. N. P. G. Edling, Dr. J. Eggert, Dr. F. K. Fischer, Dr. M. Holzmann, Dr. H. Kragenbühl, Dr. A. Lindbom, Dr. E. Lindgren, Dr. G. A. Preiss, Dr. S. Welin, and Dr. A. Zuppinger.

One would be remiss in not including a word of praise to the publishers, not only for undertaking this very important roentgenologic work, but also for the excellent volumes they have thus far produced.

This volume is highly recommended to the medical profession and especially to the diagnostic roentgenologist and the orthopedic surgeon.

R. BURNS LEWIS.

THE merit of *The Principles of Neurological Surgery*[1] which has made necessary a fourth edition rests upon a firm foundation. There is a remarkably adequate and judiciously assembled coverage of lesions affecting the brain, spinal cord, peripheral nerves, and autonomic nervous system within the confines of 534 pages as well as many excellent illustrations. Special diagnostic measures are now included such as the localization of cerebral tumours using radioactive di-iodo-fluorescein, and the Selverstone Geiger-Mueller counter brain needle. The chapter on brain abscess might well include excision among the methods of treatment, whether or not the abscess is encapsulated, and making cases with deepening coma potential emergencies.

This is an excellent book for the student, house surgeon, and practicing physician.

E. H. BOTTERELL.

[1]THE PRINCIPLES OF NEUROLOGICAL SURGERY. By Loyal Davis, M.S., M.D., Ph.D., D.Sc., (Hon.). 4th rev. ed. Philadelphia: Lea & Febiger, 1953.

WHILE written in French, the *Atlas d'hysterographie*[2] is readily translated and understood by those who use French infrequently or even not at all. The many pictures are well done and quite completely portray the many uses of this procedure. Representative pictures of the normal uterus, congenital anomalies, and tumors, both benign and malignant, are presented. A chapter on the findings in pregnancy is included. (The use of this procedure under such circumstances is questionable.)

Endometrial hyperplasia gives a characteristic picture and the findings are discussed. Endometriosis (adenomyosis) is often demonstrable by this procedure.

A distinct feature of this atlas is the fact that all of the examples shown are proved by study of the surgically removed uterus so the accuracy of the interpretations is unquestionable. Coexisting pelvic tumors can be identified by this procedure and the authors present several typical cases.

Accidental filling of the veins and lymphatics is described. This may occur despite the care taken in performing the procedure. Extension of the injected material into the peritoneal cavity and the possible hazards are delineated. To obviate this the use of an antibiotic solution with the radio-opaque material is mentioned. The apparatus and the technique are described as used by the authors.

While the frequent employment of the procedure is not indicated there are some circumstances when it can provide an advantage in diagnosis. To those who use the procedure occasionally, such an atlas as this is certain to be of great advantage because it is so inclusive in the lesions that are present.

JOHN I. BREWER.

[2]ATLAS D'HYSTEROGRAPHIE. By P. Brocq, P. Moulonguet-Doleris, R. Maricot, and H. Hartmann. 106 pages, 140 illustrations. 1.440 fr. Paris: Masson & Cie, 1953.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PLANNING GUIDE FOR RADIOLOGIC INSTALLATIONS. Wendell G. Scott, Chairman. By the Committee on Planning of Radiologic Installations of the Commission on Public Relations of the American College of Radiology. 336 pages, illustrated. $8.00. Chicago: The Year Book Publishers, Inc., 1953.

ARTRITE REUMATÓIDE. Jacques Houli. 264 pages, 44 illustrations. Rio de Janeiro, 1953.

DYSTROPHIA MUSCULORUM PROGRESSIVA; EINE GENETISCHE UND KLINISCHE UNTERSUCHUNG DER MUSKELDYSTROPHIEN. By Prof. Dr. P. E. Becker. 311 pages, 101 illustrations. DM 28.50. Stuttgart: Georg Thieme Verlag, 1953.

PRÓTESES METÁLICAS E ACRÍLICAS NAS ARTROPLASTIAS; INDIÇACÕES—TÉCNICAS E RESULTADOS TARDIOS. Prof. F. E. Godoy Moreira. 132 pages, 65 illustrations. São Paulo, 1953.

SURGERY OF REPAIR AS APPLIED TO HAND INJURIES. By B. K. Rank, M.S.(Melbourne), F.R.C.S.(England), F.R.A.C.S., and A. R. Wakefield, M.S.(Melbourne), F.R.C.S.(England), F.R.A.C.S. Foreword by Sir Gordon Gordon-Taylor. 256 pages, 188 illustrations. $8.00. Edinburgh and London: E. & S. Livingstone Ltd., 1953.

RESUSCITATION OF THE NEWBORN. By Joseph D. Russ, M.D., F.A.A.P. 55 pages, 7 illustrations. $2.50. Springfield, Ill.: Charles C Thomas, 1953.

MOTHER AND BABY CARE IN PICTURES. By Louise Zabriskie, R.N. 4th ed. 244 pages, 255 illustrations. $3.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

ESSENTIALS OF MEDICAL RESEARCH. By Wallace Marshall, M.D. 176 pages. $3.00. New York: Vantage Press, Inc., 1953.

PRAKTISCHE GEBURTSHILFE; FUER STUDIERENDE UND AERZTE. By Prof. Dr. med. Dr. phil. W. Pschyrembel. 657 pages, 458 illustrations. DM 28. Berlin: Walter de Gruyter & Co., 1953.

ARCHIVIO "PUTTI" DI CHIRURGIA DELGI ORGANI DI MOVIMENTO. Directed by O. Scaglietti. Edited by L. Gui. Vol. 3. 672 pages text, 136 pages bibliography, illustrated. Firenze, Italy: Edizioni Scientifiche dell' Instituto Ortopedico Toscano, 1953.

DIAGNOSIS OF ACUTE ABDOMINAL PAIN. By William Requarth, M.D. Foreword by Warren H. Cole, M.D. 243 pages, 79 illustrations. $5.00. Chicago, Illinois: The Year Book Publishers, Inc., 1953.

THE DIGESTIVE TRACT IN ROENTGENOLOGY. By Jacob Buckstein, M.D. 2nd ed. Vols. I and II. 1202 pages, 1,534 illustrations in 897 figures. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

HANDATLAS DER CYSTOSKOPIE UND URETHROCYSTOSKOPIE. By Dr. med. O. Kneise and Dr. Med. M. Stolze. 3rd rev. ed. 110 pages, 23 colored plates. DM 50. Leipzig: Veb Georg Thieme, 1953.

DISEASES OF WOMEN. By ten teachers under the direction of Frederick W. Roques. Edited by Frederick W. Roques, John Beattie, and Joseph Wrigley. 9th ed. 480 pages, 176 illustrations. $6.50. Baltimore: The Williams & Wilkins Co.; London: Edward Arnold & Co., 1953.

NASH'S SURGICAL PHYSIOLOGY. Revised and edited by Brian Blades, M.D. 2nd rev. enl. ed. 686 pages, 35 illustrations. $12.50. Springfield, Ill.: Charles C Thomas, 1953.

CLINICAL ROENTGENOLOGY. Vol. I—Developmental and Systemic Conditions and Local Lesions in the Extremities. By Alfred A. de Lorimier, Henry G. Moehring, and John R. Hannan. 492 pages, illustrated. $18.50. Springfield, Ill.: Charles C Thomas, 1953.

PICTORIAL INTRODUCTION TO NEUROLOGICAL SURGERY. By G. F. Rowbotham, and D. P. Hammersley. 108 pages, 81 illustrations. $4.50. Baltimore, Maryland: The Williams & Wilkins Co., 1953.

VALORES TOTALES DEL VOLUMEN SANGUINEO, HEMOGLOBINA, PROTEINAS Y LIQUIDO EXTRA-CELULAR EN CIRUGIA (tesis doctoral). By Hipolito Duran Sacristan. Director: Profesor R. Vara Lopez. 286 pages, 24 illustrations. Burgos, Spain: Secretariado de Publicaciones, Universidad de Valladolid, Facultad de Medicina, 1953.

DIE ERKRANKUNGEN DER WIRBELSAEULE. By Prof. Dr. Kurt Lindemann and Dr. Hans Kuhlendahl. 376 pages, 114 illustrations. DM 46. Stuttgart: Ferdinand Enke Verlag, 1953.

GRENZEN DES NORMALEN UND ANFAENGE DES PATHOLOGISCHEN IM ROENTGENBILDE DES SKELETTES. By Prof. Dr. A. Köhler. Revised and edited by Dozent Dr. E. A. Zimmer. 9th ed. 672 pages, 1282 illustrations. Stuttgart: Georg Thieme Verlag, 1953.

THE MEDICAL STAFF IN THE HOSPITAL. By Thomas Ritchie Ponton, B. A., M.D. 2nd ed. 373 pages. $7.25. Chicago: Physicians' Record Co., 1953.

TRIUMPH OF LOVE; AN UNFORGETTABLE STORY OF THE POWER OF GOODNESS. By Leona S. Bruckner. 213 pages. $3.00. New York: Simon & Schuster, 1954.

LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Med. Heinrich Martius. 3rd rev. ed. 414 pages, 446 illustrations. DM 49.80. Stuttgart: Georg Thieme Verlag, 1953.

EPILEPSY AND THE FUNCTIONAL ANATOMY OF THE HUMAN BRAIN. By Wilder Penfield, and Herbert Jasper. Chapter 14 by Francis McNaughton. 896 pages, 8 color plates and 314 black and white illustrations. $16.00. Boston: Little, Brown & Co., 1954.

CORRESPONDENCE

THE SURGICAL SIGNIFICANCE AND MANAGEMENT OF PATHOLOGIC BLOOD CLOTTING—A CORRECTION

To the Editor: I should like to correct an error which I made in my article entitled, "The Surgical Significance and Management of Pathologic Blood Clotting," published in the November 1953 issue of SURGERY, GYNECOLOGY AND OBSTETRICS. On page 593, last line, column 1, the sentence should read: "Lack of vitamin K increases the bleeding tendency"; substituting the word "bleeding" for the word "clotting."

Sincerely yours,

GERALD H. PRATT

November 24, 1953